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Coriatone and Corianlactone, Two Novel Sesquiterpenes from *Coriaria nepalensis*

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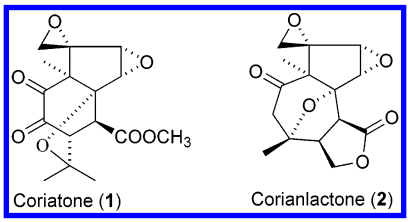
ABSTRACT



Both coriatone (1), a novel highly oxygenated picrotoxane-type sesquiterpene, and corianlactone (2), with an unprecedented sesquiterpene basic skeleton, named coriane, were isolated from *Coriaria nepalensis* Wall. The structures of 1 and 2 were determined by analysis of their two-dimensional NMR data, and the structure of 2 was confirmed by X-ray analysis. Compounds 1 and 2 showed no remarkable inhibitory activity toward K_{562} cells. They are cytotoxic with IC_{50} > 50 μg/mL (*cis*-platinim: IC_{50} = 0.49 μg/mL).

Coriaria nepalensis Wall is a Chinese herbal medicine that has been used to treat numbness, toothache, traumatic injury, and acute conjunctivitis.[1] Until now, several similar sesquiterpene lactones have been isolated from plants belonging to the family Coriariaceae[2−5] and *Loranthus parasiticus* Merr[6] (a parasitic plant that grows on the twigs of *Coriaria sinica* Maxim), which are mainly distributed in the southern and southwestern parts of China and are used to treat schizophrenia[7] in southwest China. Among these sesquiterpene lactones, coriamytin and tutin were considered as main bioactive ingredients for treatment of schizophrenia.[8] During our investigation on a new and potentially bioactive sesquiterpene lactone from *C. nepalensis*, two novel sesquiterpenes, including one unprecedented sesquiterpene skeleton, were isolated from the aerial parts of this plant. This paper elucidates the structures of coriatone (**1**) and corianlactone (**2**) with both spectroscopic data and single-crystal X-ray analysis.

Dried aerial parts (7 kg) of *C. nepalensis* collected in the Kunming region of Yunnan Province were percolated in 95% EtOH (25 L × 3). The extract was concentrated in vacuo, and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated producing a residue (106 g), which was chromatographed over silica gel eluting with a petroleum ether−acetone (1:0−0:1) gradient system to afford fractions 1−9. Fraction four was subjected to column chromatography over MCI-gel CHP-20P (MeOH−H_2O, 9:1) to yield a yellow

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(1) *Dictionary of Traditional Chinese Medicine*; Shanghai People Press: 1977; p 294.
(2) Okuda, T.; Yoshida, T. *Chem. Pharm. Bull.* **1967**, *15*, 1955−1965.
(3) Okuda, T.; Yoshida, T. *Tetrahedron Lett.* **1971**, *47*, 4499−4502.
(4) Liang, X.-Y.; Chen, H.-L.; Xiao, X.; Zhou, J.-F.; Cai, X.-X.; Zhang, B.-Z.; Huang, Y.-H.; Cao, Y.-H.; Chen, X.-M.; Li, L.-Q.; Lu,T.-P. *Zhong Cao Yao Tong Xun* (in Chinese) **1978**, *10*, 1−4.
(5) Wei, H.; Zeng, F.-J.; Lu, M.-Y.; Tang, R.-J. *Acta Pharm. Sinica* (in Chinese) **1998**, *33*, 688−692.
(6) Okuda, T.; Yoshida, T.; Chen, X.-M.; Xie, J.-X.; Fukushima, M. *Chem. Pharm. Bull.* **1987**, *35*, 182−187.
(7) Yuan, D.-J. *Zhonghua Shenjingjingshenke Zazhi* (in Chinese) **1979**, *12*, 196−199.
(8) Chen, X.-M. *Zhong Cao Yao Tong Xun* (in Chinese) **1977**, *11*, 34−37.

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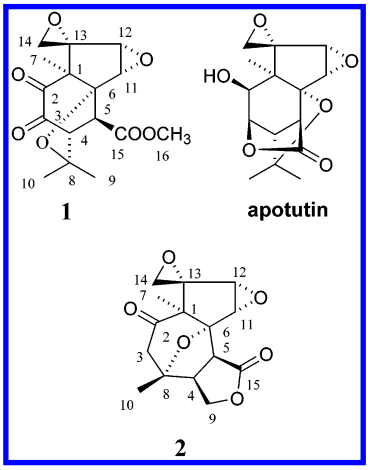

crystalline product, coriatone (**1**) (15 mg). Fraction eight was also purified by column chromatography over MCI-gel CHP-20P (MeOH−H_2O, 9:1) to give a colorless crystalline product, corianlactone (**2**) (17 mg).

Coriatone (**1**), [α]D 25.3−16.13° (*c* 0.155, MeOH), was isolated as a yellow crystalline whose molecular formula of $C_{16}H_{18}O_7$ was established on the basis of EIMS and ^{13}C and DEPT NMR spectra and confirmed by HRESIMS analysis ($[M + H]^+$ *m*/*z* 323.1127, calcd 323.1130). Thus, the structure of **1** possessed eight degrees of unsaturation. The UV spectrum (MeOH) showed end adsorption. The ^{13}C and DEPT NMR spetrum displayed signals for 16 carbons, which contained four methyls (including one carboxymethyl), one oxygenated methylene, four methines (including oxygenated ones), and seven quaternary carbons (including two ketone carbonyl carbons, one ester carbonyl, and three oxygenated sp^3 carbons), which exhibited a highly oxygenated sesquiterpene skeleton.

Detailed comparison of ^1H and ^{13}C NMR (see Table 1) data of **1** with those of apotutin[5] displayed extreme analogy. The ^1H NMR spectrum of **1** displayed an AB quartet at δ_H 4.22 (1H, d, J = 3.0 Hz) and 3.62 (1H, d, J = 3.0 Hz), which is analogous to the epoxide protons at C-11 and C-12 of apotutin; another AB quartet at δ_H 3.27 (1H, d, J = 5.0 Hz) and 2.98 (1H, d, J = 5.0 Hz) is analogous to the terminal epoxide protons at C-14 in apotutin, and the carbon signals at δ_C 88.7 (s) and 83.9 (s) are similar to the ether ring of apotutin connected C-6 to C-8. An isopropyl at C-4 similar to apotutin was confirmed by HMBC correlations from Me-9 (δ_H 1.43) and Me-10 (δ_H 1.28) to C-8 and C-4. Thus, the above spectroscopic analogies between **1** and apotutin strongly suggested that **1** possessed a structure similar to apotutin, on the same carbon skeleton.

The following were the differences between **1** and apotutin: Oxygenated methines of apotutin at C-2 and C-3 were replaced by two ketone carbonyl that were shifted downfield to δ_C 192.7 and 191.5, which was consistent with the absence of H-2 and H-3 in ^1H NMR spectrum of **1**. One methyloxy at δ_C 53.0 revealed the opening of the γ-lactone ring located at the C-3 to C-5 of apotutin and formation of carboxymethyl group connective to C-5 in **1**, which was supported by HMBC (see Table 1**)** correlations between OMe-16 (δ_H 3.65, s) and C-15 (δc 171.2, s) and between H-5 (δ_H 4.27, d, J = 4.0 Hz) and C-15. The assignment of δ_C 192.7 for C-2 resulted from the correlation of Me-7 (δ_H 1.69, s) with C-2 in the HMBC spectrum. The HMBC cross-peaks from H-4 and H-5 to δ_C 191.5 (C-3) determined the placement of C-3.

Table 1. ^1H and ^{13}C NMR Assignments and HMBC Correlations of **1**[a]

no.	δ_H (mult, J, Hz)	δ_C (mult)	HMBC (H−C)	ROESY (H−H)
1		51.3 (s)		
2		192.7 (s)		
3		191.5 (s)		
4	3.51 (d, 4.0)	59.8 (d)	2, 3, 5, 6, 9	5, 9, 10
5	4.27 (d, 4.0)	52.3 (d)	1, 3, 4, 6, 11, 15	4, 9
6		88.7 (s)		
7	1.69 (s)	20.9 (q)	1, 2, 6, 13	10
8		83.9 (s)		
9	1.43 (s)	30.4 (q)	4, 8, 10	4, 5, 10
10	1.28 (s)	25.9 (q)	4, 8, 9	7, 9
11	4.22 (d, 3.0)	57.7 (d)	1, 6, 13	12, 16
12	3.62 (d, 3.0)	57.2 (d)	1, 6, 13	11,14b
13		64.0 (s)		
14a	3.27 (d, 5.0)	49.4 (t)	12, 13	14b
14b	2.98 (d, 5.0)		12, 13	12, 14a
15		171.2(s)		
16	3.65 (s)	53.0 (q)	15	11β-H

[a] Data were recorded in C_5D_5N on Bruker AM-400 MHz (^1H, ^{13}C) and Bruker DRX-500 MHz spectrometers (HMBC, ROESY); chemical shifts (δ) are given in parts per million.

The stereochemical relationship among the functional groups, i.e., the spiro epoxide ring at C-13, the epoxide ring between C-11 and C-12, and the ether bridge at C-6−O−C-8 and Me-7, has been established to be identical with that of apotutin by REOSY analysis (see Table 1) and also by comparison of chemical shifts and coupling constants of **1** with those of apotutin. The relative configuration of H-5 was determined as α-orientation on the basis of its small coupling (J = 4.0 Hz) with H-4 and its REOSY correlations with Me-9 and H-4. The cross-peak of OMe-16 with 11β-H further confirmed the α-orientation of H-5.

Corianlactone (**2**), $[\alpha]_D$ 26.3−162.5° (*c* 0.12, MeOH), crystallized as a colorless prism and has the molecular formula of $C_{15}H_{16}O_6$ as determined by analysis of ^1H, ^{13}C, and DEPT NMR spectral data (see Table 2), which was verified by HRESI MS ($[M + H]^+$ *m*/*z* 293.1033, calcd 293.1025), possessing eight degrees of unsaturation. The ^{13}C NMR spectrum of **2** exhibited signals for 15 carbons assigned to a highly oxygenated sesquiterpene skeleton differed from **1**.

The ^1H NMR spectrum of **2** showed an AB quartet at δ_H 4.17 (1H, d, J = 3.2 Hz) and 3.64 (1H, d, J = 3.2 Hz) analogous to the epoxide protons at C-11 and C-12 of **1**. Another AB quartet for a pair of geminal protons at δ_H 4.33 (1H, d, J = 5.0 Hz) and 3.25 (1H, d, J = 5.0 Hz) was similar to that observed in the spiro epoxide ring system at C-13 of **1**. A detailed comparison of ^{13}C NMR data of **2** with those of **1** indicated that **2** possessed the same five-membered ring

Table 2. ^{1}H and ^{13}C NMR Assignments and HMBC Correlations of **2**

no.	δ_H (mult, J, Hz)	δ_C (mult)	COSY	HMBC (H−C)	ROESY (H−H)
1		51.7 (s)			
2		203.4 (s)			
3α	2.92 (d, 17.1)	44.3 (t)	3β	2, 4, 8, 10	3β, 7, 10
3β	2.63 (d, 17.1)		3α	1, 2	3α, 9β
4	3.13 (m)	50.8 (d)	5, 9	3, 5, 8, 10, 15	5, 7, 9α
5	4.01 (d, 11.5)	55.1 (d)	4	4, 6, 8, 15	4, 11
6		89.7 (s)			
7	1.83 (s)	22.8 (q)		1, 2, 6, 13	3α, 4
8		87.8 (s)			
9α	4.36 (dd, 10.5, 2.5)	66.9 (t)	4, 9β	8, 15	4
9β	4.32 (dd, 10.5, 7.5)		4, 9α	8, 15	3β
10	1.43 (s)	24.3 (q)		3, 4, 8	3α
11	4.17 (d, 3.2)	58.4 (d)	12	1, 6	12
12	3.64 (d, 3.2)	57.1 (d)	11	1, 13	11, 14b
13		62.6 (s)			
14a	4.33 (d, 5.0)	51.1 (t)	14b	1, 12, 13	14b
14b	3.25 (d, 5.0)		14a	12, 13	12, 14a
15		173.8 (s)			

[a] Data were recorded in C_5D_5N on Bruker AM-400 MHz (^{1}H, ^{13}C) and Bruker DRX-500 MHz spectrometers (COSY, HMBC, ROESY); chemical shifts (δ) are given in parts per million.

fragment substituted by a spiro epoxide ring and an epoxide ring as in **1**.

The ^{13}C NMR chemical shifts for the remaining portion of the structure of **2** were quite distinctive from those of **1**, and Me-10 (δ_H 1.43, s) showed HMBC correlations (see Table 2) with δ_C 44.3 (C-3, t), δ_C 50.8 (C-4, d), and δ_C 87.8 (C-8, s). A reasonable interpretation of the above observations is that C-3 was connected with C-4 via C-8 and formed a seven-membered ring with C-1, C-2, C-5, and C-6, which was supported by HMBC spectral data. A γ-lactone ring between C-4 and C-5 was established by the spin coupling system among H-4, H-5, and H-9 from analysis of COSY spectrum, along with the HMBC correlation of H-9α (δ_H 4.36, dd, J = 10.5, 2.5 Hz) and H-9β (δ_H 4.32, dd, J = 10.5, 7.5 Hz) with 173.8 (C-15, s). Thus, the above inferences led to a seven-membered ring substituted by a γ-lactone ring between C-4 and C-5 in **2**, rather than the similar six-membered ring in **1**.

The connectivity between the above five-membered ring and the seven-membered ring was determined by the HMBC correlation of 14a-H, Me-7, and 3β-H with C-1 and of H-11 and H-5 with C-6. The ether ring of C-6−O−C-8 was established by comparison of the chemical shifts of **2** with those of **1** and verified by X-ray diffraction (see Figure 1).[9] Me-10 (1.43, s) was linked to C-8 via a HMBC cross-peak with δ_C 87.8 (C-8, s), together with HMBC correlations of H-3α (2.92, d, J = 17.1 Hz) and H-4 (3.13, m) with δ_C 24.3 (C-10, s). Thus, the structure of **2** was elucidated as a novel sesquiterpene with five- and seven-membered rings possessing an unprecedented basic skeleton. The relative stereochemistry of **2** was determined by two-dimensional REOSY experiment (see Table 2) and confirmed by X-ray diffraction study (see Figure 1).[9]

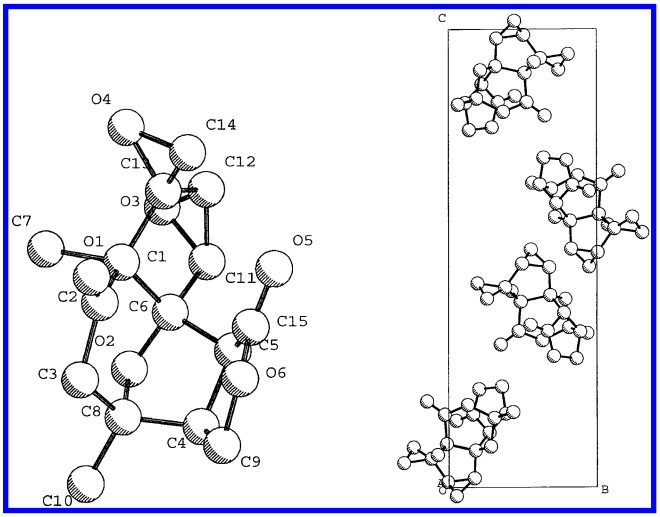

Figure 1. X-ray structure of **2**.

The novel carbon skeleton of corianlactone (**2**), which we named coriane, represents a new class of sesquiterpene. It is the first example with the coriane-type sesquiterpene skeleton.

Compounds **1** and **2** were tested for cytotoxicity toward K_{562} cells using the same bioassay methods as previously described in the literature,[10] and neither compound has remarkable inhibitory activity with $IC_{50} > 50$ μg/mL (*cis*-platinim: $IC_{50} = 0.49$ μg/mL).

Supporting Information Available: Tabulated NMR data for **1** and **2** and NMR spectra for **1** and **2** in C_5D_5N. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Crystal data: $C_{15}H_{16}O_6$, M = 292.29, orthorhombic system, space group $P2_12_12_1$, a = 7.301 (1), b = 7.580 (1), c = 23.430 (3) Å, V = 1296.7 (3) Å^3, Z = 4, d = 1.497 g/cm^3. A crystal of dimensions 0.30 × 0.40 × 0.60 mm was used for measurements on a MAC DIP-2030K diffractometer with a graphite monochromator (ω-2θ scans, $2\theta_{max}$ = 50.0°), Mo Kα radiation. The total number of independent reflections measured was 1434, of which 1136 were observed ($|F|^2 \geq 8\sigma|F|^2$). The crystal structure was solved by the direct method SHELX-86 (Sheldrick, G. M.; University of Gottingen: Gottingen, Germany, 1985) and expanded using difference Fourier techniques, refined by the program and method NOMCSDP (Lu, Y.; Wu, B. M. *Chin. Chem. Lett.* **1992**, *3*, 637−640) and full-matrix least-squares calculations. Final indices: R_f = 0.057, R_w = 0.061 ($w = 1/\sigma|F|^2$). Crystallagraphic data for the structure of **2** has been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 235021). Copies of these data can be obtained, free of charge, on application to the CCDC via www.ccdc.com.ac.uk/conts/retrieving.html (or 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

(10) Niu, X.-M.; Li, M.-L.; Zhao, Q.-S.; Mei, S.-X.; Na, Z.; Wang, S.-J.; Lin, Z.-W.; Sun, H.-D. *Planta Med.* **2002**, *68*, 528−33.