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Jatrophalactam, A Novel Diterpenoid Lactam Isolated from *Jatropha curcas*

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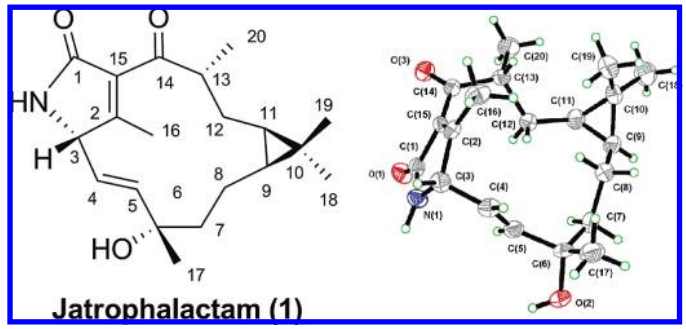
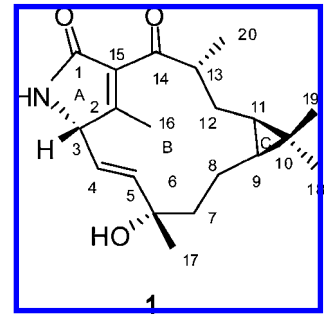
ABSTRACT



Jatrophalactam (1), a novel diterpenoid lactam possessing an unprecedented 5/13/3 tricyclic skeleton, was isolated from the roots of *Jatropha curcas*. The structure and relative configuration of jatrophalactam (1) were elucidated by extensive spectroscopic analysis and further determined by a single-crystal X-ray diffraction.

Jatropha curcas Linn. (Euphorbiaceae) is a native of tropical America but now thrives in many parts of the tropics and subtropics in Africa/Asia. It is a plant with many attributes, multiple uses, and considerable potential. This plant can be used to prevent and/or control erosion, used to reclaim land, grown as a live fence, especially to contain or exclude farm animals, and planted as a commercial crop.[1] The oil from *J. curcas* seeds can be used externally for the treatment of sciatica, dropsy, paralysis, rheumatism, and certain skin diseases.[2] Besides, the seeds contain 30% oil that can be processed to produce a high-quality biodiesel fuel, usable in a standard diesel engine. Previous investigations on the genus *Jatropha* had revealed that diterpenoid was their major secondary metabolite, and some of the diterpenoids were cytotoxic and tumor-inhibitory constituents.[3−7]

One of our efforts to discover the structurally diverse and biologically significant metabolities from plant resources has led to the isolation of jatrophalactam (**1**), a novel diterpenoid lactam possessing an unprecedented skeleton from the roots of *Jatropha curcas*. Herein we report the isolation and structural elucidation of **1**.



The dried and powdered roots of *J. curcas* (3 kg) were extracted with MeOH at room temperature three times, which

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afforded a dark residue (245 g) after evaporation under reduced pressure. The residue was suspended in H_2O and then partitioned with petroleum ether and EtOAc successively. The EtOAc extract (35 g) was subjected to a MCI gel column chromatography eluted with MeOH−H_2O (20:80 to 100:0) to give six fractions A−F. Fraction D (10.2 g) was chromatographed over a silica gel column and then an RP-18 column to yield jatrophalactam (**1**, 35 mg).

Compound **1**[8] was obtained as a colorless crystal. Its molecular formula, $C_{20}H_{29}NO_3$, was established on the basis of HREIMS for the $[M]^+$ at *m*/*z* 331.2153, which indicated seven degrees of unsaturation. The IR spectrum showed characteristic absorptions for OH (3392.2 cm^{-1}), NH (3266.9 cm^{-1}), and C═O (1704.8 cm^{-1}) functions. The ^{13}C NMR of **1** showed 20 carbon signals that were sorted by DEPT experiments into two carbonyls, four olefinic carbons, five methyls, three methylenes, four methines, and two quaternary carbons (Table 1). The ^1H NMR showed the presence of

Table 1. ^1H and ^{13}C NMR Data of **1** in $CDCl_3$ (300 and 75 MHz, Respectively)

position	δ_H (mult, *J* in Hz)	δ_C
1		171.9 (qC)
2		131.0 (qC)
3	4.56 (d, 3.3)	60.3 (CH)
4	5.75 (dd, 16.2, 3.3)	123.8 (CH)
5	5.84 (d, 16.2)	138.1 (CH)
6		73.7 (qC)
7	1.33 (m), 1.77 (m)	42.2 (CH_2)
8	1.58 (m)	20.0 (CH_2)
9	0.53 (m)	27.0 (CH)
10		18.4 (qC)
11	0.43 (m)	21.8 (CH)
12	1.42 (m), 1.48 (m)	28.4 (CH_2)
13	2.45 (m)	47.7 (CH)
14		205.8 (qC)
15		157.4 (qC)
16	2.01 (s)	14.7 (CH_3)
17	1.28 (s)	22.1 (CH_3)
18	0.98 (s)	29.4 (CH_3)
19	0.89 (s)	15.6 (CH_3)
20	1.26 (d, 7.2)	13.7 (CH_3)
NH	7.00 (brs)	

five methyl signals at δ_H 2.10 (s), 1.28 (s), 1.26 (d, $J = 7.2$ Hz), 0.98 (s), 0.89 (s), and *trans*-double bond signals at δ_H 5.83 (d, $J = 15.9$ Hz) and 5.75(dd, $J = 15.9$, 3.3 Hz) (Table 1).

Comprehensive analysis of the $^1H-^1H$ COSY spectrum of **1** allowed the establishment of two structural fragments as drawn with bold lines in Figure 1. From the molecular

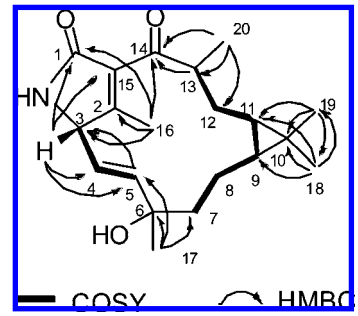

Figure 1. Key $^1H-^1H$ COSY and HMBC correlations of **1**.

formula of **1**, we can see that it possessed a nitrogen atom, and in the HSQC spectrum, a proton at δ_H 7.00 (brs), which had no correlations with the C-atom, was assigned to be an active hydrogen of the NH group. The HMBC spectrum (Figure 1) allowed us to establish the A ring system of **1** to be an α,*β*-unsaturated five-membered lactam cycle from the following correlations: δ_H 7.00 (brs, NH) correlated with C-1(δ_C 171.9), C-2 (δ_C 131.0), C-3 (δ_C 60.3), and C-15 (δ_C 157.4); δ_H 4.56 (d, $J = 3.3$ Hz, H-3) correlated with C-1, C-4 (δ_C 123.8), C-5 (δ_C 138.1), and C-15 (δ_C 157.4); an allyl methyl, appeared at δ_H 2.01 (s, H_3-16), correlated with C-1, C-2, C-3, C-14 (δ_C 205.8), and C-15. The other four methyls were assigned by the key HMBC correlations observed from H_3-17 (δ_H 1.28, s) to C-5 (δ_C 138.1), C-6 (δ_C 73.7), and C-7 (δ_C 42.2); and from H_3-18 (δ_H 0.98, s) to C-9 (δ_C 27.0), C-10 (δ_C 18.4), C-11 (δ_C 21.8), and C-19 (δ_C 15.6); and from H_3-19 (δ_H 0.89, s) to C-9, C-10, C-11, and C-18 (δ_C 29.4); and from H_3-20 (δ_H 1.26, d, $J = 7.2$ Hz) to C-12 (δ_C 28.4), C-13 (δ_C 47.7), and C-14 (δ_C 205.8). The HMBC connectivity from H-3 to C-4, C-5, and from H-4 (δ_H 5.75, dd, $J = 15.9$, 3.3 Hz) and H-5 (δ_H 5.83, d, $J = 15.9$ Hz) to C-3 accounted for the double bond substituted on C-3. The cross peaks of H_3-16/C-14 and H-13/C-14 furnished the connection of the carbonyl (C-14) to the A ring. Hence the planar structure of **1** was determined as a novel diterpenoid lactam possessing an unprecedented 5/13/3 tricyclic skeleton.

The relative configuration of **1** was assigned by a ROESY spectrum (Figure 2), in which the correlations of H-3/H_3-16, H-4/H_3-16, H-4/H_3-17, H-13/H_3-16, H_3-16/H_3-19, H-13/H_3-19, H-12*β*/H-13, and H-12*β*/H_3-19 indicated that they were cofacial and arbitrarily fixed in *β*-orientation. So the 6-OH and H_3-20 were both in α-orientation. The other ROESY correlations of H-9/H_3-18, H-11/H_3-18, H-11/H-12α, and H-8α/H-9 indicated that they were α-oriented. This conclusion was finally confirmed by the performance of a single-crystal X-ray diffraction of **1**.[9] The conformation of **1** in solution as established by ROESY spectrum was in good

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(8) Jatrophalactam (**1**): $C_{20}H_{29}NO_3$, colorless crystal (EtOAc), mp 185−186 °C; $[\alpha]_D^{20}$ + 148.7 (*c* 0.3, MeOH); IR (KBr) ν_{max} 3392, 3266, 2933, 2969, 1704, 1664, 1457, 1384, 1093, 985 cm^{-1}; ^1H and 9C NMR see Table 1; ESI-MS *m*/*z* 332.2 $[M + H]^+$, 685.4 $[2M + Na]^+$, 330.1 $[M - H]^-$; HREIMS *m*/*z* 331.2153 $[M]^+$ (calcd for $C_{20}H_{29}NO_3$, 331.2147).

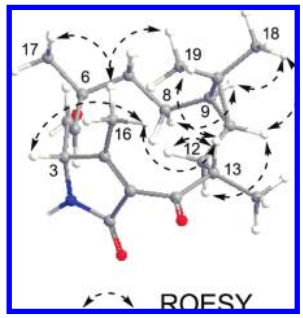

Figure 2. Key ROESY correlations of **1**.

agreement with that in the solid state as determined by X-ray study (Figure 3).

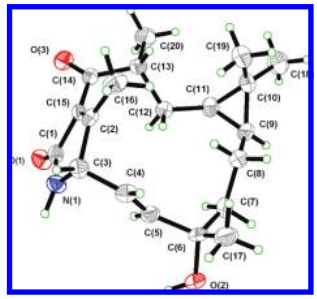

Figure 3. Single-crystal X-ray structure of **1**.

Compound **1** was the first novel diterpenoid lactam possessing an unprecedented 5/13/3 tricyclic framework. It is presumably biosynthesized from the biogenetically acceptable diterpenoid, casbene, which was distributed widely on the genus *Jatropha*. A plausible biogenetic pathway for **1** was proposed (Supporting Information).

The in vitro cytotoxic activity of compound **1** was evaluated against three human cancer cell lines, A549 (human lung cancer), HT-29 (human colon cancer), and A431 (human epidermal squamous cell carcinoma). Compound **1** displayed no significant inhibitory activity on these three cell lines.

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Supporting Information Available: Experimental procedures, 1D and 2D NMR spectra, MS spectra, and X-ray crystallographic data in CIF format of jatrophalactam (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Crystallographic data of compound **1**: $C_{20}H_{29}NO_3$, MW = 331.44, monoclinic, space group *P*2(1); a = 6.872 (4), b = 9.187 (5), c = 15.595 (9) Å, α = 90.00, β = 97.384 (9), γ = 90.00, V = 976.4 (10) Å^3, Z = 2, ρ_{calc} = 1.127 g/cm^3, crystal dimensions 0.02 × 0.07 × 0.10 mm was used for measurement on a Bruker APEX SMART-CCD diffractometer with a graphite monochromater. The total number of reflections measured was 4813, of which 3157 were observed, $I > 2\sigma(I)$. Final indices: R = 0.0702, wR2 = 0. 1990. The crystal structure of **1** was solved by direct method SHLXS-97 (Sheldrick, 1990) and expanded using difference Fourier technique, refined by the program SHLXL-97 (Sheldrick, 1997) and the full-matrix least-squares calculations. Crystallographic data for compound **1** have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 743516). Copies of the data can be obtained, free of charge, on application to the director, CCDC 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).