Jatrophenone, a Novel Macrocyclic Bioactive Diterpene from *Jatropha gossypifolia*[1)]

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A novel macrocyclic diterpene, jatrophenone, has been isolated from the whole plant of *Jatropha gossypifolia*. The structure of the compound was established by detailed studies of its one- and two-dimensional (1D and 2D) NMR spectra. The compound possesses significant antibacterial activity.

Key words *Jatropha gossypifolia*; jatrophenone; macrocyclic diterpene; antibacterial activity

Jatropha gossypifolia LINN (Euphorbiaceae) grows wild in different parts of India. The plant is known[2)] to possess various medicinal and pesticidal properties. Earlier investigation on the plant resulted[3—5)] in the isolation of several bioactive diterpenes and lignans. During our present work on its constituents we have discovered a novel macrocyclic diterpene, jatrophenone (**1**) from the CH_2Cl_2–MeOH (1 : 1) extract of the whole plant. Here we report the structure elucidation and bioactivity of the compound **1**.

Jatrophenone (**1**) was obtained as a white solid. Its molecular formula was deduced to be $C_{22}H_{30}O_4$ from its mass spectrum ($[M+Na]^+$: *m/z* 381 in liquid secondary ionization mass spectrometry (LSI-MS)), elemental analysis and ^{13}C-NMR spectrum. The IR spectrum of the compound (ν_{max}^{KBr}: 1730, 1718, 1595 cm^{-1}) indicated the presence of ester and ketone carbonyls as well as unsaturation in the molecule. Its ^{1}H-NMR spectrum (Table 1) suggested that it contains a disubstituted *trans*-double bond (δ 5.58, 1H, dd, J=6.0, 9.5 Hz and 5.12, 1H, dd, J=16.0, 9.5 Hz) along with an exocyclic (δ 4.80, 1H, s and 4.78, 1H, s) and a trisubstituted double bonds (δ 5.77, d, J=9.5 Hz). The spectrum also revealed the presence of an acetoxy (δ 2.09, 3H, s) and four methyl groups [δ 1.72 (3H, s), 1.15 (6H, s), 1.02 (3H, s)], one of which is vinylic. The ^{13}C-NMR spectrum presented the signals for twenty carbons along with those for an acetoxy group (δ 176.8, 21.3) (Table 1). The spectrum in assistance with APT (Attached Proton Test) experiment showed that besides the acetoxy group the molecule possesses two keto carbonyls, three double bonds, four methyls, two methylenes and six methines. The configuration of the trisubstituted double bond was assigned *trans* (*E*) by comparing the ^{13}C-NMR values of the two double bonded carbons (C-4, C-5) with those reported earlier for the corresponding carbons of other trisubstituted double bonds present in different diterpenes.[6,7)]

The structure of jatrophenone (**1**) was unambiguously settled from the analysis of its two-dimensional (2D) NMR (^{1}H–^{1}H correlation spectroscopy (COSY), ^{1}H-detected heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple bond connectivity (HMBC) and nuclear Overhauser effect spectroscopy (NOESY)) spectra. The protonated carbons were assigned from ^{1}H–^{1}H COSY and HMQC measurements while the quaternary carbons from APT and HMBC experiments (Table 1). The last experiment was particularly useful to determine the structure of **1**. It showed that H_2-1 were related to C-3, C-4, C-14 and C-16 while H-3 to C-1, C-5, C-15 and acetyl carbonyl group. These data indicate that C-4 and C-15 are linked forming a cyclopantane ring found occasionally in diterpenes of *Jatropha* species.[3,8,9)] The acetoxy group was thus also kept at C-3. The other ring present in the molecule is 11-membered and its functionalities were placed by following the HMBC experiment. The trisubstituted double bond was assigned at C-4, C-5 as C-4 showed correlation to H-1 and H-2 and C-5 to H-3 and H-15 while the disubstituted *trans* (*E*) double bond was assigned at C-11, C-12 as H-12 was related to C-14 (which was related to one of the protons at C-1 (as discussed earlier) and the methyl protons at C-20) and H-11 to C-13 containing the same methyl group (Me-20). The other methyl group (Me-17) was reasonably placed at C-6 because this methyl carbon showed correlation with the olefinic proton at C-5. The protons of this methyl group (H_3-17) were also related to C-5 and a carbonyl group placed at C-7. Additionally, the olefinic proton at C-11 was related to a carbon (C-10) containing an exocyclic methylene group (H_2-19) and another methyl group (Me-18) relating to C-9. The last position was readily identified by observing that the attached proton (H-9) showed correlation with C-12 and the carbonyl group at C-7. The position C-8 was found to be occupied by two protons which are connected to C-10 and C-11. Thus the structure of jatrophenone was established as **1**.

The NOESY experiment was carried out to determine the stereochemistry of **1** (Fig. 1). The methyl at C-2 was placed with β-configuration as the proton at C-2 and C-15 showed clearly the NOE correlation. On the other hand the acetoxy group at C-3 is β-oriented because the H-3 was not related to H-2 and H-15 but was related to H_3-16. Similarly, by following the NOE correlations the protons at C-9 and C-13 were assigned to be β while that at C-6α.

Molecular dynamics for the energy minimized conformation of **1** were carried out using Insight II program on a Silicon Graphics work station. The CVff force field with default parameters were used throughout the simulations. Minimizations were done first with steepest decent, followed by conjugate gradient methods for a maximum of 1000 iterations each. A 50 psec MD run at 300 K temperature was studied and the conformation for each and every 1000 fsec were sampled. The collected conformations were minimized using the above mentioned procedure. Out of those 50 conformations one of the minimum energy conformation of **1** (Fig. 2), was consistent with NOE studies.

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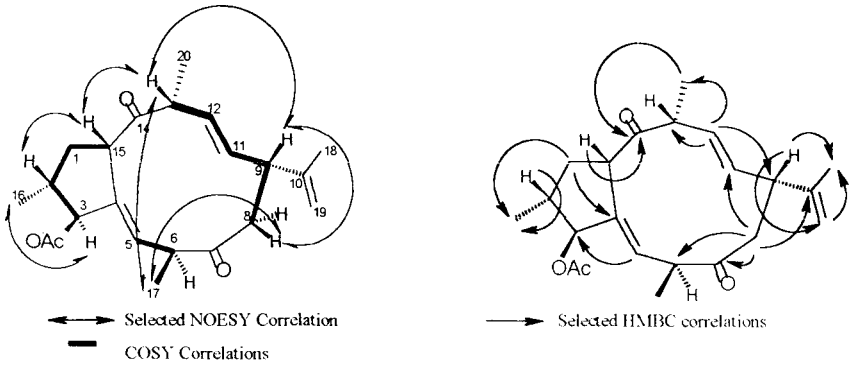

Fig. 1. Jatrophenone (**1**)

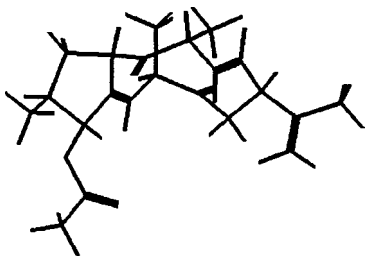

Fig. 2. Energy Minimized Diagram of **1**

In a preliminary study[10] jatrophenone (**1**) was found to possess antibacterial activity against the organism, *Staphylococcus aureus*. Its activity was comparable to that of the standard compound, penicillin G.

Experimental

General The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Unity INOVA 500 MHz spectrometer with standard pulse sequences, operating at 500 and 125 MHz respectively, and using tetramethylsilane (TMS) as an internal standard. The IR spectra was recorded on Perkin-Elmer RXI FT-IR spectrophotometer and mass spectra on Finnigan-MAT 1020. Optical rotation was measured on a JASCO DIP-370 polarimeter.

Extraction and Isolation The air dried and powdered plant material (2 kg) was extracted thrice with CH_2Cl_2–MeOH (1 : 1)–each extraction was continued for 72 h. The total extract was concentrated to a gummy brown mass (22 mg). This was subjected to column chromatography over silica gel using hexane–EtOAc as eluent. The fraction eluted with hexane–EtOAc (5 : 1) was concentrated and rechromatographed to produce a solid which crystallized from MeOH to yield jatrophenone (**1**) (24 mg, yield 0.0012%).

Jatrophenone (**1**): mp, 204—205 °C; $[\alpha]_D^{25}$ −4.5° (c=0.5, MeOH); IR (KBr) ν_{max} 1730, 1718, 1595 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Table 1; LSI-MS m/z: 382 $[M+Na]^+$; *Anal.* Calcd for $C_{22}H_{30}O_4$. C, 73.71; H, 8.43. Found C, 73.68; H, 8.44%.

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Table 1. NMR Spectral Values of Jatrophenone (**1**) in $CDCl_3$ (δ in ppm)

Position	δ_H [a]	δ_C [b]	HMBC [c]
1	1.85, m	36.9	C-4, C-14, C-15, C-16
	2.10, m		C-2, C-3, C-4, C-14, C-15
2	2.05, m	37.4	C-1, C-3, C-4, C-16
3	5.27, d	91.0	C-1, C-5, C-15, acetyl >CO
	(J=10.2 Hz)		
4		140.0	
5	5.77, d	139.7	C-3, C-15, C-17
	(J=9.5 Hz)		
6	3.36, m	48.9	C-4, C-5, C-7, C-17
7		210.4	
8	2.75, t	46.2	C-6, C-7, C-10, C-11
	(J=10.5 Hz)		
	2.40, dd		C-6, C-7, C-10, C-11
	(J=10.5, 3.5 Hz)		
9	2.85, m	46.8	C-8, C-10, C-12, C-18, C-19
10		145.9	
11	5.58, dd	134.2	C-8, C-9, C-10, C-13
	(J=16.0, 9.5 Hz)		
12	5.12, dd	131.2	C-9, C-13, C-14, C-20
	(J=16.0, 9.5 Hz)		
13	3.30, m	53.4	C-11, C-14, C-20
14		211.0	
15	3.65, t	51.2	C-2, C-3, C-4, C-5, C-14
	(J=4.5 Hz)		
16	1.02, d	13.6	C-1, C-3
	(J=6.0 Hz)		
17	1.15, d	16.8	C-5, C-6, C-7
	(J=4.5 Hz)		
18	1.72, s	21.3	C-9, C-10, C-19
19	4.80, s	110.1	C-9, C-10, C-18
	4.73, s		C-9, C-10, C-18
20	1.15, d	17.7	C-12, C-13, C-14
	(J=4.5 Hz)		
–OCOCH$_3$	2.09, s	170.8	
		21.3	

a) Supported by ^{1}H–^{1}H COSY experiments. *b*) Supported by ATP, HMQC and HMBC experiments. *c*) Protons related to carbons.

References and Notes

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10) The detailed bioactivity data will be published elsewhere.