Two New Pentacyclic Triterpenoids from *Lantana camara* Linn.

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Two new pentacyclic triterpenoids, namely lantanoic acid (1) and camaranoic acid (2), and six known compounds such as lantic acid, camarinic acid, camangeloyl acid, camarinin, oleanonic acid, and ursonic acid were isolated from the aerial parts of *Lantana camara* Linn. Structures of the new constituents were elucidated by chemical transformation and spectral studies including 1D (^{1}H- and ^{13}C-NMR) and 2D (^{1}H–^{1}H correlation spectroscopy (COSY), nuclear Overhauser effect spectroscopy (NOESY), ^{1}H–^{1}H total correlation spectroscopy (TOCSY), *J*-resolved, ^{1}H-detected heteronuclear multiple quantum coherence (HMQC), and heteronuclear multiple bond connectivity (HMBC)) NMR spectroscopy.

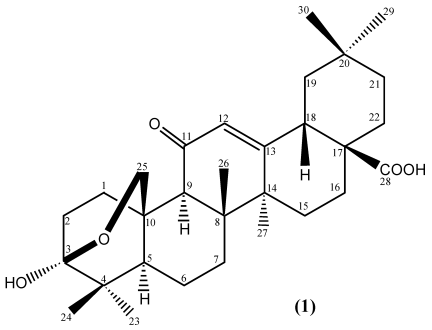
Key words *Lantana camara*; Verbenaceae; pentacyclic triterpenoid; lantanoic acid; camaranoic acid

Lantana camara Linn. (family: Verbenaceae), commonly known as lantana, is a hairy shrub, native of Tropical America cultivated elsewhere as an ornamental or hedge plant. Different parts of the plant are used for the treatment of various human ailments, such as itches, cuts, ulcers, malaria, influenza, anemia, tumors, swellings, bilious fever, eczema eruptions, rheumatism, stomachache, toothache, scabies, and leprosy and as antiseptic for wounds. Aqueous extract of the leaves showed antihyperglycaemic activity and wound-healing property. Pharmacological investigations indicated that extracts of the shoot of *L. camara* exhibit antibacterial properties. Lancamarone, a steroid from the leaves, possesses cardiotonic property, whereas lantamine, an alkaloid from the bark of stems and roots, shows strong antipyretic and antispasmodic properties comparable with those of quinine.[1—4] Phytochemical studies undertaken by several groups on different parts of the plant have resulted in the isolation of various terpenoids,[3,5] steroids,[3] and flavonoids.[3,6] The present studies were undertaken on the chemical constituents of the aerial parts of this plant, which resulted in the isolation and structure elucidation of two new triterpenoids, lantanoic acid (**1**) and camaranoic acid (**2**), along with six known triterpenoids, lantic acid,[7] camarinic acid,[8] camangeloyl acid,[9] camarinin,[10] oleanonic acid,[11] and ursonic acid.[12]

Results and Discussion

Compound **1** displayed a molecular ion peak at *m*/*z* 484.3178 in the HR-EI-MS, in agreement with the molecular formula $C_{30}H_{44}O_5$. The IR spectrum of **1** showed absorption bands at 3450—2640 (br OH and COOH), 1700 (acid C=O), 1690 (α,β unsaturated ketone C=O), and 1120 cm^{-1} (C–O) and a UV maximum at 250 nm. It formed the methyl ester (**1a**; δ_H 3.58, s; Table 2) on reaction with diazomethane confirming the presence of a carboxyl group in the molecule. Analysis of the ^{1}H- and ^{13}C-NMR spectra of **1** revealed six methyl signals as singlets (δ_H 1.32, 1.02, 0.96, 0.91, 0.90, 0.84) and an olefinic singlet (δ_H 5.65, H-12) (Table 1). These signals indicated a pentacyclic triterpenoidal skeleton in **1**. The ^{1}H-NMR further showed a double doublet at δ_H 2.96 (J=13.4, 3.7 Hz) attributed to H-18, characteristic of Δ^{12} oleanane-type skeleton.[8] A quick inspection of the ^{1}H- and ^{13}C-NMR spectra of the compound confirmed the presence of a β-oriented hemiacetal system at C-3 with C-25 in compound **1** [δ_H 4.52 (1H, br d, J=8.3 Hz, H-25a), δ_H 4.03 (1H, br d, J=8.3 Hz, H-25b); δ_C 65.7; CH_2, distortionless enhancement by polarization transfer (DEPT); ^{1}H-detected heteronuclear multiple quantum coherence (HMQC)]. Interaction between H-25a and H-25b and of both these protons with H-1b in the ^{1}H–^{1}H-correlation spectroscopy (COSY) spectrum due to long-range coupling as suggested earlier by various authors[13] for this system was also observed. Connectivities of H-25a with C-5 and of H-25b with C-10 in the heteronuclear multiple bond connectivity (HMBC) spectrum supported this system (Table 1).

A one-proton olefinic singlet at δ_H 5.65 and the UV spectrum of **1** (λ_{max} at 250 nm) suggested the presence of α-β-unsaturated carbonyl function at C-11, which was confirmed by carbon signals in the ^{13}C-NMR spectrum at δ 127.8 (C-12), 169.4 (C-13) and 198.4 (C-11).[14] The presence of this ketonic moiety at C-11 was further confirmed by a downfield shift of H-1a (δ_H 3.02), which is comparable with other 11-keto compounds.[14,15] A weak interaction of H-12 with H-18 in the ^{1}H–^{1}H-COSY spectrum and the connectivities of H-9 with C-8, C-10, C-11, C-25, and C-26 and of H-12 with C-9,



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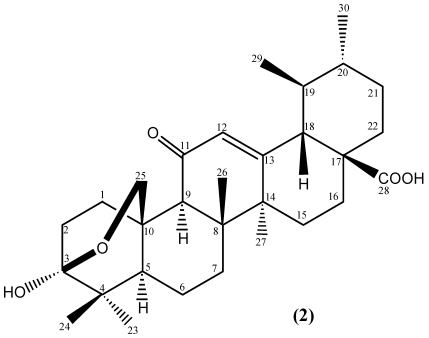

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Table 1. ^{1}H- (400 MHz) and ^{13}C- (125 MHz) NMR Data of Compounds **1** and **2** ($CDCl_3$ in ppm, *J* in Hz)

1					**2**				
No. C	C-type	δ_H (*J*)	δ_C	HMBC (H→C)	No. C	C-type	δ_H (*J*)	δ_C	HMBC (H→C)
1	CH_2	a: 3.02 ddd (12.3, 12.3, 4.7) b: 1.16 m	34.6	C-2, C-3, C-5, C-10	1	CH_2	a: 2.95 ddd (12.6, 12.6, 4.7) b: 1.17 m	34.7	C-2, C-3, C-5, C-10, C-25
2	CH_2	a: 2.11 m b: 1.76 m	29.3		2	CH_2	a: 2.12 m b: 1.76 m	29.3	
3	C		98.7		3	C		98.5	
4	C		40.7		4	C		40.7	
5	CH	1.20 m	51.1		5	CH	1.17 m	51.1	
6	CH_2	a: 1.54 m b: 1.48 m	19.1		6	CH_2	a: 1.53 m b: 1.46 m	19.1	C-5, C-8
7	CH_2	a: 1.52 m b:1.36 m	30.8	C-5, C-9	7	CH_2	a: 1.51 m b: 1.37 m	31.0	C-5, C-8, C-9
8	C		43.6		8	C		43.5	
9	CH	2.43 s	55.4	C-8, C-10, C-11, C-25, C-26	9	CH	2.42 s	55.3	C-8, C-10, C-11, C-25, C-26
10	C		35.1		10	C		35.0	
11	C=O		198.4		11	C=O		198.1	
12	CH	5.65 s	127.8	C-9, C-14, C-18	12	CH	5.62 s	130.6	C-9, C-13, C-14, C-18
13	C		169.4		13	C		163.5	
14	C		43.8		14	C		43.8	
15	CH_2	a: 1.62 m b: 1.31 m	28.1		15	CH_2	a: 1.77 m b: 1.32 m	28.7	C-13
16	CH_2	a: 2.03 m b: 1.71 m	22.9	C-15, C-17, C-28 C-15, C-17	16	CH_2	a: 2.06 m b: 1.76 m	23.9	C-15, C-17, C-18, C-28
17	C		45.9		17	C		47.4	
18	CH	2.96 dd (13.4,3.7)	41.8	C-12, C-13, C-14, C-16, C-17	18	CH	2.38 d (11.8)	52.9	C-12, C-13, C-14, C-16, C-17, C-19, C-28, C-29
19	CH_2	a: 1.59 m b: 1.18 m	44.3	C-13, C-18, C-20, C-30 C-17, C-20, C-21, C-30	19	CH	1.36 m	38.8	C-18, C-20, C-29, C-30
20	C		30.8		20	CH	0.94 m	38.6	
21	CH_2	a: 1.36 m b: 1.25 m	33.6		21	CH_2	a: 1.56 m b: 1.31 m	30.3	C-17, C-20 C-17
22	CH_2	a: 1.76 m b: 1.63 m	31.4	C-16, C-17, C-21, C-28	22	CH_2	a: 1.78 m b: 1.64 m	35.8	C-16, C-17, C-18, C-20, C-21, C-28 C-16, C-17, C-20, C-21, C-28
23	CH_3	1.02	27.4	C-3, C-4, C-5, C-24	23	CH_3	1.02 s	27.4	C-3, C-4, C-5, C-24
24	CH_3	0.96	18.4	C-3, C-4, C-5, C-23	24	CH_3	0.97 s	18.5	C-3, C-4, C-5, C-23
25	CH_2	a: 4.52 br d (8.3) b: 4.03 br d (8.3)	65.7	C-5 C-10	25	CH_2	a: 4.59 br d (8.2) b: 4.04 br d (8.2)	65.8	C-5 C-5, C-10
26	CH_3	0.84 s	19.1	C-7, C-8, C-9, C-14	26	CH_3	0.83 s	19.1	C-7, C-8, C-9, C-14
27	CH_3	1.32 s	23.1	C-13, C-14, C-15	27	CH_3	1.27 s	21.0	C-8, C-13, C-14, C-15
28	COOH	11.65	180.7		28	COOH	11.68	180.6	
29	CH_3	0.90 s	32.8	C-19, C-20, C-21, C-30	29	CH_3	0.84 d (6.1)	17.0	C-18, C-19, C-20
30	CH_3	0.91 s	23.3	C-19, C-20, C-21, C-29	30	CH_3	0.94 d (6.2)	20.7	C-19, C-20, C-21, C-29
3	OH	2.67 br s			3	OH	2.64 br s		

Assignments are based on ^{1}H-, ^{13}C-NMR (broad band decoupled, DEPT), ^{1}H–^{1}H COSY, ^{1}H–^{1}H TOCSY, NOESY, *J*-resolved, HMQC and HMBC.

C-14, and C-18 in the HMBC spectrum (Table 1) supported this assignment.

Furthermore, a fragment ion at *m/z* 262.1562 appeared in the mass spectrum of **1** resulting from retro-Diels–Alder fragmentation[16] of ring C indicating a carboxylic group (ν_{max} 3450—2640, 1700 cm^{-1}) at C-14 or C-17 of **1**. Comparison of ^{13}C-NMR chemical shift data of rings D and E with the published values of compounds having similar structures[17] confirmed its position at C-17. The remaining oxygen function was placed in ring A as part of the hemiacetal system. Since C-25 forming the epoxide linkage with C-3 is β-oriented, the hydroxyl group was given an α-disposition. Stereochemistry at various centres was confirmed by significant nuclear Overhauser effect spectroscopy (NOESY) interactions (Fig. 1). On the basis of the above data the structure of **1** was assigned as 3,25-epoxy-3α-hydroxy-11-oxo-olean-12-en-28-oic acid.

The HR-EI-MS of compound **2** showed a molecular ion peak at *m/z* 484.3175, corresponding to the molecular formula $C_{30}H_{44}O_5$. Its IR spectrum showed absorption bands at 3450—2643 (br OH and COOH), 1700 (acid C=O), 1691 (α,β unsaturated ketone C=O), and 1122 cm^{-1} (C–O) and a UV maximum at 248 nm. The ^{1}H-NMR spectrum of **2** (Table 1) showed six methyl signals, four as singlets at δ_H 1.27, 1.02, 0.97, and 0.83 and two as doublets at δ_H 0.84 (*J*=6.1 Hz) and 0.94 (*J*=6.2 Hz). The ^{1}H-NMR spectrum also showed resonance for an olefinic proton at δ_H 5.62 (s, H-12) and a characteristic[18] methine proton at δ_H 2.38 (d,

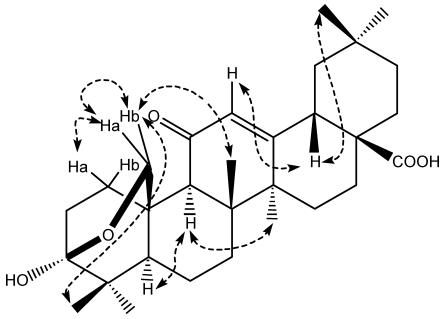

Fig. 1. Significant NOESY (◀⋯▶) Interactions of (**1**)

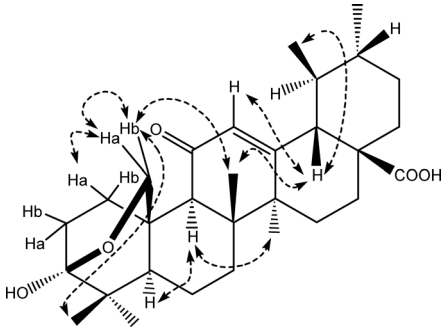

Fig. 2. Significant NOESY (◀⋯▶) Interactions of (**2**)

Table 2. ^{1}H-NMR Data of **1a** and **2a** ($CDCl_3$ in ppm, *J* in Hz)

1a			**2a**		
No. C	C-type	δ_H (*J*)	No. C	C-type	δ_H (*J*)
1	CH_2	a: 3.00 ddd (12.4, 12.4, 4.6)	1	CH_2	a: 2.96 ddd (12.5, 12.5, 4.8)
		b: 1.16 m			b: 1.16 m
2	CH_2	a: 2.11 m	2	CH_2	a: 2.12 m
		b: 1.76 m			b: 1.77 m
5	CH	1.20 m	5	CH	1.18 m
6	CH_2	a: 1.54 m	6	CH_2	a: 1.52 m
		b: 1.48 m			b: 1.47 m
7	CH_2	a: 1.52 m	7	CH_2	a: 1.53 m
		b: 1.36 m			b: 1.38 m
9	CH	2.44 s	9	CH	2.44 s
12	CH	5.64 s	12	CH	5.60 s
15	CH_2	a: 1.62 m	15	CH_2	a: 1.78 m
		b: 1.31 m			b: 1.31 m
16	CH_2	a: 2.03 m	16	CH_2	a: 2.07 m
		b: 1.71 m			b: 1.76 m
18	CH	2.97 dd (14.2, 4.1)	18	CH	2.39 d (11.7)
19	CH_2	a: 1.59 m	19	CH	1.37 m
		b: 1.18 m			
21	CH_2	a: 1.36 m	20	CH	0.95 m
		b: 1.25 m	21	CH_2	a: 1.57 m
22	CH_2	a: 1.76 m			b: 1.30 m
		b: 1.63 m	22	CH_2	a: 1.78 m
23	CH_3	1.01	23	CH_3	1.01 s
24	CH_3	0.95	24	CH_3	0.98 s
25	CH_2	a: 4.53 br d (8.2)	25	CH_2	a: 4.57 br d (8.3)
		b: 4.03 br d (8.2)			a: 4.03 br d (8.3)
26	CH_3	0.83 s	26	CH_3	0.84 s
27	CH_3	1.33 s	27	CH_3	1.27 s
29	CH_3	0.91 s	29	CH_3	0.84 d (6.1)
30	CH_3	0.92 s	30	CH_3	0.96 d (6.2)
	$COOCH_3$	3.58 s		$COOCH_3$	3.61 s
3	OH	2.66 br s	3	OH	2.65 br s

J=11.8 Hz, H-18). These data indicated that **2** belongs to the Δ^{12} α-amyrin series of pentacyclic triterpenoids.

Spectroscopic analysis further indicated that compound **2** is the ursane isomer of compound **1** from the following observations: a β-oriented hemiacetal system at C-3 with C-25 [δ_H 4.59 (1H, br d, *J*=8.2 Hz, H-25a), δ_H 4.04 (1H, br d, *J*=8.2 Hz, H-25b); δ_C 65.8, CH_2, DEPT, HMQC], a Δ^{12}-11-one functionality [δ_H 5.62, 1H, s, H-12, UV λ_{max} 248 nm, and IR ν_{max} 1691 cm^{-1}; δ_C 130.6, C-H, DEPT, H-12, 163.5, C-13 and 198.1, C-11 (Table 1)] and a COOH group at C-17 indicated by the IR (*loc. cit*) and ^{13}C-NMR (δ_C 180.6) and confirmed by methylation (CH_2N_2) to **2a** (OCH_3 δ_H 3.61 s; Table 2) and ^{13}C-NMR data of ring D and E (Table 1). On the basis of the above spectral data, the structure of **2** was assigned as 3, 25-epoxy-3α-hydroxy-11-oxo-urs-12-en-28-oic acid. The above assignments were made by 2D-NMR studies including ^{1}H–^{1}H COSY, NOESY (Fig. 2), HMQC, and HMBC (Table 1) and the structure was finally corroborated by mass fragmentation pattern.

The known compounds have been identified through comparison of their spectral data with those of the corresponding constituents reported in the literature.

Experimental

UV spectra were measured by Hitachi U-3200 spectrophotometer. IR spectra were obtained on a Jasco A-302 spectrophotometer in $CHCl_3$. ^{1}H-NMR (^{1}H–^{1}H COSY, NOESY, ^{1}H–^{1}H TOCSY, and *J*-resolved) and ^{13}C-NMR spectra were measured on a Bruker Avance spectrometer at 600 MHz for ^{1}H- and 150 MHz for ^{13}C-NMR. Chemical shifts are reported relative to TMS and coupling constants (*J*) are expressed in Hz. EI-MS and HR-EI-MS (70 eV) were recorded on a Finnigan-MAT 311A and Jeol JMS-HX-110 mass spectrometer, respectively. HPLC was carried out using preparative recycling HPLC Jaigel LC 908W equipped with a variable-wavelength UV detector UV-S310A, model II and differential refractometer RI-5. Vacuum liquid chromatography (VLC) was carried out on Merck silica gel 60 PF_{254}. Flash column chromatography (FCC) was performed on Eyela Flash Column EF-10 chromatograph using silica gel 9385 (Merck, 0.040—0.063 mm). Prep. TLC was carried out over silica gel 60 PF_{254} (Merck). Analytical (thin layer) chromatography was performed on Kieselgel Si F_{254} precoated aluminum cards (0.2 mm thickness, Merck) and TLC plates were visualized under UV light or by spraying with iodine.

Extraction and Isolation of Compounds from *Lantana camara* Aerial parts of *L. camara* were collected from the Karachi region. The plant was identified by Mr. Abdul Ghafoor, Senior Taxonomist, Department of Botany, University of Karachi and a voucher specimen (No. 63482 KUH) is deposited in the Herbarium.

Air-dried aerial parts of *Lantana camara* (10 kg) were repeatedly extracted with methanol at room temperature. The concentrated extract obtained on removal of the solvent from the combined extract under reduced pressure was partitioned between EtOAc and H_2O. The EtOAc phase was treated with 4% aqueous solution of Na_2CO_3 to separate the acidic from the neutral fraction. The EtOAc layer containing the neutral fraction was washed with water, dried (Na_2SO_4), and passed through active charcoal.

The charcoal bed was successively washed with EtOAc and MeOH–C_6H_6 (1 : 1), which were combined on the basis of TLC. The residue obtained on removal of the solvent from the EtOAc layer and washings was divided into petroleum ether-soluble and -insoluble fractions. The latter fraction was further divided into ether-soluble and -insoluble fractions. The latter fraction was again divided into EtOAc-soluble and -insoluble portions. The EtOAc-soluble fraction (40 g) was subjected to VLC ($CHCl_3$; $CHCl_3$–MeOH in order of increasing polarity), which ultimately furnished 9 fractions (Fr-1 to Fr-9) on combining the eluates on the basis of TLC.

Fr-1 (26.0 g) ($CHCl_3$, $CHCl_3$–MeOH, 9.9 : 0.1 eluates) was again subjected to VLC (petroleum ether; petroleum ether–EtOAc in order of increasing polarity), which ultimately furnished 8 fractions (Fr-I to Fr-VIII) on combining the eluates on the basis of TLC. Fr-III (5.6 g) obtained on elution with petroleum ether–EtOAc (8 : 2, 7 : 3 eluates) was subjected to flash CC ($CHCl_3$–MeOH in increasing order of polarity), which furnished one pure compound, lantic acid (3.0 mg) ($CHCl_3$–MeOH, 9.8 : 0.2 eluate), along with

a major fraction Fr-III-5 ($CHCl_3$–MeOH, 9.7 : 0.3 eluate). Fr-III-5 was subjected to preparative recycling HPLC on SIL-10-A-06 column using an isocratic mixture of $CHCl_3$–IPA (9.6 : 0.4) as mobile phase at a flow rate of 4 ml/min. Camangeloyl acid (7.0 mg), lantanoic acid (**1**; 4.5 mg), and camaranoic acid (**2**; 5.0 mg) were obtained after 4 recycling operations with t_R 40, 45, and 50 min, respectively.

Fr-V (2.2 g) (petroleum ether–EtOAc, 6 : 4 eluates) was subjected to CC ($CHCl_3$–MeOH, in order of increasing polarity), which ultimately furnished twelve fractions (Fr-l to Fr-12). Fr-l0 ($CHCl_3$–MeOH, 9.8, 0.2 eluates) was subjected to recycling HPLC on SIL-10-A-06 column using an isocratic mixture of $CHCl_3$–IPA (9.6 : 0.4) as an eluent at a flow rate of 2.5 ml/min. Lantanoic acid (**1**; 1.0 mg) and camaranoic acid (**2**; 1.5 mg) were isolated after 4 recycling operations with t_R 45 and 50 min, respectively, along with camarinic acid (6.0 mg, t_R 15 min). Fr-11 ($CHCl_3$–MeOH, 9.7, 0.3 eluates) was also subjected to preparative recycling HPLC on Jaigel 1H+2H column using $CHCl_3$ as eluent at a flow rate of 3.5 ml/min and afforded camarinin (3.0 mg) after 2 recycling operations with t_R 30 min.

In another working, the petroleum ether-insoluble fraction was subjected to vacuum liquid chromatography (VLC; petroleum ether; petroleum ether–EtOAc in order of increasing polarity). On pooling together the fractions on the basis of TLC, fourteen fractions (LC-1 to LC-14) were obtained. Fraction LC-3 (3.0 g), which was eluted with petroleum ether–EtOAc (8 : 2), was again subjected to VLC (petroleum ether; petroleum ether–EtOAc in order of increasing polarity), which ultimately furnished eleven fractions (F-1 to F-11). Fraction F-3 (petroleum ether–EtOAc, 9.25 : 0.75 eluate) on keeping overnight at room temperature in $CHCl_3$–MeOH (1 : 1) afforded a colourless crystallizate, which on separation through TLC ($CHCl_3$–MeOH, 9.9 : 0.1; run three times) afforded oleanonic acid (6.0 mg) and ursonic acid (5.0 mg).

Lantanoic Acid (1) Amorphous powder; $[\alpha]_D^{28}$ +158.4° (c=0.14, in $CHCl_3$). UV λ_{max} (MeOH): 250 nm. IR (KBr): ν_{max} cm^{-1}. 3450—2640 (br OH and COOH), 1700 (acid C=O), 1690 (α,β unsaturated ketone C=O) and 1120 (C–O) cm^{-1}. ^{1}H- and ^{13}C-NMR: see Table 1. EI-MS *m*/*z* (%): 484 [M^+] (10), 466 (13), 421 (l00), 262 (16), 257 (13), 221 (33), 187 (6), 133 (10), 119 (15), 105 (24) and 69 (42). HR-EI-MS *m*/*z*: 484.3178 [$C_{30}H_{44}O_5$, M^+; Calcd for $C_{30}H_{44}O_5$, 484.3189].

Methylation of 1 Compound **1** (2.2 mg) furnished the methyl derivative **la** (2.0 mg) on treatment with an ethereal solution of CH_2N_2 and usual workup. ^{1}H-NMR ($CDCl_3$): δ_H 3.58 (COOMe). EI-MS *m*/*z*: 498 (M^+).

Camaranoic Acid (2) Amorphous powder; $[\alpha]_D^{28}$ +153.0° (c=0.15, in $CHCl_3$). UV λ_{max} (MeOH): 248 nm. IR (KBr): ν_{max} cm^{-1}. 3450—2643 (br OH and COOH), 1700 (acid C=O), 1690 (α,β unsaturated ketone C=O) and 1122 (C–O) cm^{-1}. ^{1}H- and ^{13}C-NMR: see Table 2. EI-MS *m*/*z* (%): 484 [M^+] (12), 466 (21), 421 (100), 262 (18), 257 (15), 221 (28), 187 (6), 133 (13), 119 (17), 105 (26) and 69 (47). HR-EI-MS *m*/*z* 484.3175 [$C_{30}H_{44}O_5$, M^+; Calcd for $C_{30}H_{44}O_5$, 484.3189].

Methylation of 2 Compound **2** (2.0 mg) furnished the methyl derivative **2a** (1.7 mg) on treatment with an ethereal solution of CH_2N_2 and usual workup. ^{1}H-NMR ($CDCl_3$): δ_H 3.61 (COOMe). EI-MS *m*/*z*: 498 (M^+).

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