

TWO NEW PENTACYCLIC TRITERPENOIDS FROM THE AERIAL PARTS OF *LANTANA CAMARA* LINN

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Abstract– Two new constituents camarolide (**1**) and lancamaric acid (**4**) along with two known compounds oleanonic acid (**2**) and ursonic acid (**3**) have been isolated from the aerial parts of *Lantana camara* Linn. Structures of the new compounds have been established as 3-keto-urs-11-en-13 β (28)-olide (**1**) and 3,25-epoxy-3 α -ethoxy-olean-12-en-28-oic acid (**4**) through spectral studies including 1D (^1H -, ^{13}C -NMR) and 2D (COSY-45, NOESY, *J*-resolved, HMQC and HMBC) NMR.

Lantana camara L. (Verbenaceae) commonly known as lantana is a hairy shrub, native of tropical America and cultivated as an ornamental or hedge plant. Its different parts are reputed to be of use in traditional medicine for the treatment of various human ailments such as ulcers, eczema eruptions, malaria and rheumatism.¹ Pharmacological investigations have indicated that extracts of the shoots of *L. camara* exhibit antibacterial properties.¹ Lancamarone, a steroid from the leaves, possesses cardiotonic properties, while lantamine, an alkaloid from the stem and root bark, shows strong antipyretic and antispasmodic properties comparable with those of quinine.^{1,2} Phytochemical studies undertaken by different groups of workers on different parts of the plant have resulted in the isolation of various steroids, terpenoids, and flavonoids.³⁻⁵ In view of the pharmacological properties of *L. camara*, 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 pentacyclic triterpenoids, camarolide (**1**) and lancamaric acid (**4**), and two known compounds, oleanonic acid (**2**) and ursonic acid (**3**)

RESULTS AND DISCUSSION

The molecular formula of compound (**1**), $\text{C}_{30}\text{H}_{44}\text{O}_3$ (M^+ 452.3268), was obtained through HREIMS. Its IR spectrum showed bands at 2920, 2850 (CH), 1755 (lactone C=O), 1700 (ketone C=O), 1620 (C=C) and 1130 cm^{-1} (C-O). The UV spectrum showed absorption band at 210 nm indicating the lack of conjugation in the molecule. The ^1H - and ^{13}C -NMR data of **1** indicated that it belongs to α -amyrin type of triterpenoids. Thus its ^1H -NMR spectrum showed five tertiary methyl signals at δ 0.93, 1.02, 1.04, 1.08 and 1.16 and two secondary methyls at δ 0.92 (d, $J=6.3$ Hz) and 0.99 (d, $J=6.2$ Hz). It further showed two olefinic (1620 cm^{-1}) one-proton double doublets at δ 5.95 ($J=10.5$, 1.3 Hz) and 5.57 ($J=10.5$, 3.0 Hz) correlated with δ_{C} 132.7 (C-11) and δ_{C} 129.4 (C-12) respectively⁶ in the HMQC spectrum and assigned to H-11 and H-12 respectively (Table 1). These protons showed connectivities with H-9 in the COSY-45 spectrum (Figure 1). These assignments were confirmed through HMBC interactions (Figure 2). It may be noted that H-12 showed larger coupling ($J=3.0$ Hz) with H-9 as the allylic CH (at C-9) bond is perpendicular to the C=C plane, whereas coupling between H-9 and H-11 is smaller ($J=1.3$ Hz) as the dihedral angle between these CH bonds is about 90° as observed in the Dreiding model of the molecule.⁷ The presence of quaternary carbon signals in the ^{13}C -NMR spectrum (br band) at δ 89.2 (C-13) and δ 179

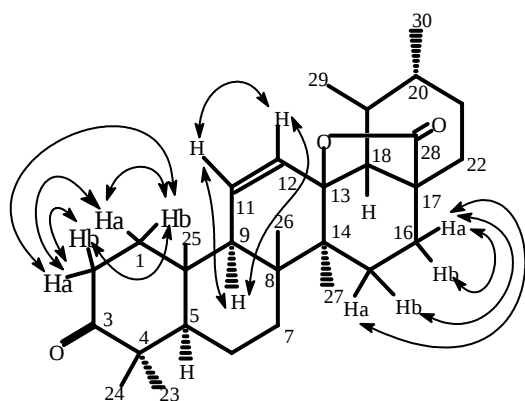


Figure 1. Significant ^1H , ^1H COSY Interactions of Camarolide (**1**)

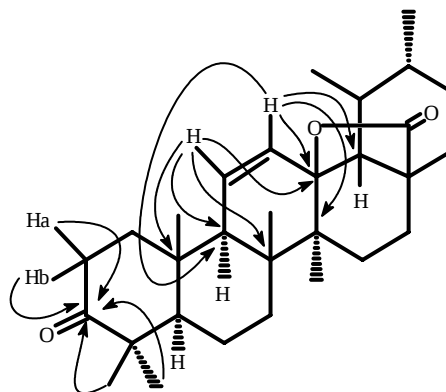


Figure 2. Significant HMBC Interactions of Camarolide (**1**)

(C-28) along with a prominent $\text{M}^+ - \text{CO}_2$ peak at m/z 408.3268 in the HREIMS indicated a lactone moiety (1755 cm^{-1}) between C-13 and C-28.⁸ The peaks at m/z 202.1658 and 69.0687 in the HREIMS confirmed this moiety⁹ (Figure 3). The IR spectrum (1700 cm^{-1}) and ^{13}C NMR signal (δ_{C} 217.5, br band) also indicated¹⁰ the presence of a carbonyl group in the molecule which was placed at C-3 on biogenetic grounds, and verified by the presence of down field signals¹⁰ at δ 2.61 (1H, m, H-2a) and δ 2.43 (1H, m, H-2b) and connectivities of the carbonyl carbon (δ_{C} 217.5) with H-2a, H-2b, as well as with H-23 and H-24 (Figure 2). From the data recorded above the structure of **1** was elucidated as 3-keto-urs-11-en-13 β (28)-olide. It may be noted that δ_{C} values assigned to C-11 and C-12 of **1** were comparable with those of reported values⁶ for ursolic acid lactone acetate whereas δ_{H} values, unambiguously assigned to these protons in the present studies on the basis of HMQC and HMBC experiments are reverse from the reported values.⁶ Compound (**1**) has been synthesized earlier from ursolic acid.^{11,12}

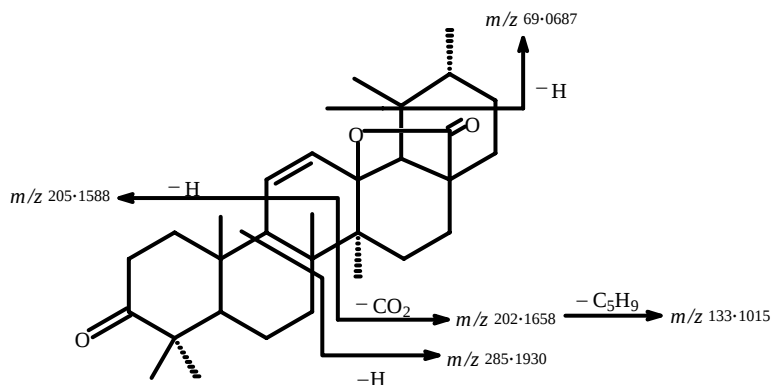


Figure 3. Significant Mass Fragmentation of Camarolide (**1**)

Table 1. ¹H- and ¹³C- NMR Spectral Data of Compound (1) (CDCl₃).

	δ _C	DEPT	δ _H	m	<i>J</i> (Hz)		δ _C	DEPT	δ _H	m	<i>J</i> (Hz)
1	39.7	CH ₂	2.06 (1a) 1.45 (1b)	m m	-	16	22.8	CH ₂	2.10 (16a) 1.40 (16b)	m m	-
2	34.1	CH ₂	2.61 (2a) 2.43 (2b)	m m	-	17	45.0	C	-	-	-
3	217.5	C	-	-	-	18	60.7	CH	1.64	d	12.0
4	47.3	C	-	-	-	19	38.2	CH	1.78	m	-
5	54.8	CH	0.83	m	-	20	40.3	CH	0.87	m	-
6	17.2	CH ₂	1.58	m	-	21	30.9	CH ₂	1.57	m	-
7	31.2	CH ₂	1.56	m	-	22	31.4	CH ₂	1.84	m	-
8	41.6	C	-	-	-	23	26.1	CH ₃	1.08	s	-
9	51.9	CH	2.04	dd	3.0, 1.3	24	20.8	CH ₃	1.02	s	-
10	36.4	C	-	-	-	25	19.6	CH ₃	0.93	s	-
11	132.7	CH	5.95	dd	10.5, 1.3	26	19.1	CH ₃	1.04	s	-
12	129.4	CH	5.57	dd	10.5, 3.0	27	16.1	CH ₃	1.16	s	-
13	89.2	C	-	-	-	28	179.0	C	-	-	-
14	42.5	C	-	-	-	29	17.8	CH ₃	0.99	d	6.2
15	25.6	CH ₂	1.72 (15a) 1.20 (15b)	m m	-	30	18.1	CH ₃	0.92	d	6.3

Assignments are based on ¹H, ¹H COSY, NOESY, *J*-resolved, HMQC and HMBC experiments.

The molecular formula, C₃₂H₅₀O₄, of compound (4) was obtained through HREIMS (M⁺, 498.3677). It showed IR absorption bands at 3450-2650 (br, COOH), 1700 (acid C=O) and 1620 (C=C) cm⁻¹ while its UV spectrum showed an absorption maximum at 205 nm. The ¹H-NMR spectrum showed six three-proton singlets at δ 0.74, 0.88, 0.97, 1.01, 1.05 and 1.10 attributable to six methyls located on quaternary carbons. It also displayed resonances for an olefinic proton (δ 5.27, t, *J*=3.5 Hz, H-12) and a characteristic ¹³C methine proton at δ 2.81 (dd, *J*=13.8, 4.4 Hz, H-18) (Table 2). These data along with the characteristic ¹³C-NMR chemical shifts of C-12 and C-13 at δ 122.6 and 143.6, respectively¹⁴ suggested that 4 belongs to the Δ¹² β-amyrin series of pentacyclic triterpenoids. Compound (4) formed the methyl derivative (4a) (δ OMe 3.57) on reaction with diazomethane confirming the carboxyl function indicated by the IR spectrum. The comparable ¹³C-NMR data^{15,16} of ring D and E with similar skeletons having COOH group at C-17 as well as characteristic retro-Diels-Alder fragments⁹ of 4 at *m/z* 248.1794, 203.1786 and 133.1011 (Figure 4) indicated the location of the carboxylic group at C-17 and the remaining oxygen function in ring A/B. Furthermore, the ¹H-NMR spectrum exhibited a pair of double doublets centred at δ 4.26 (*J*=8.4, 2.3 Hz) and 3.86 (*J*=8.4, 1.1 Hz) for the two non-equivalent methylene protons of the 3,25 epoxy function. This region of the ¹H-NMR spectrum showed a close similarity with that of lantanilic acid,¹⁷ thus ascribing these signals to H-25a and H-25b. These assignments were confirmed from cross peaks in the ¹H-¹H-COSY spectrum (Figure 5), which showed interactions between H-25a and H-25b and the interactions of both these protons with H-1b showing a long range coupling of these protons with H-1 as suggested¹⁷ earlier by various authors for this system.

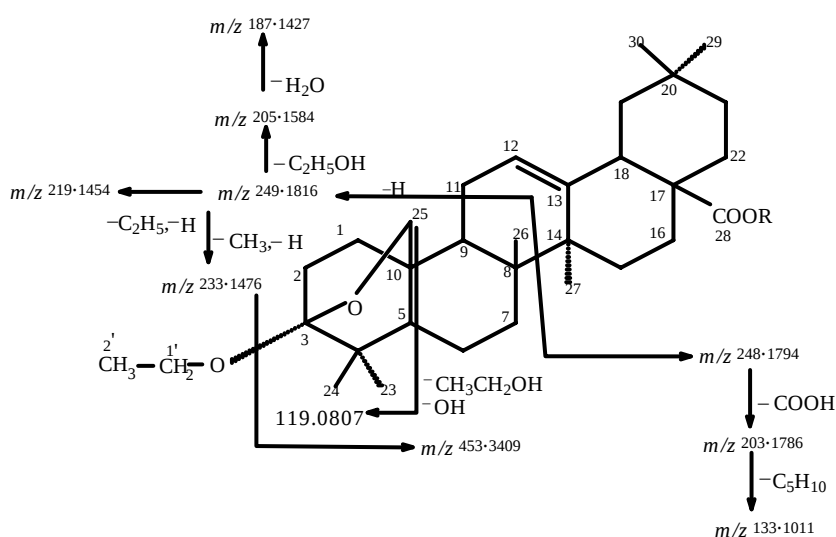


Figure 4. Significant Mass Fragmentation of Lancamaric Acid (**4**), R=H
4a, R= CH₃

The ¹H- NMR spectrum showed the presence of an ethoxy group (δ 3.71, 2H, q, $J=7.0$ Hz, H-1'; δ 1.00, 3H, t, $J=7.0$ Hz, H-2') which was confirmed by the ¹³C-NMR (DEPT) and HMQC interactions (Table 2). It was located at C-3 since the compound had no further carbinyl proton in the ¹H-NMR spectrum and was supported by fragments at m/z 249.1816, 205.1584 and 187.1427 (Figure 4) in the mass spectrum and by interactions of H-1' with C-3 (δ 100.4) in the HMBC spectrum. The HMBC spectrum also showed interactions of H-25b, H-23 and H-24 with C-3 (Figure 6). Therefore, the remaining oxygen function was placed in ring A as a part of ketal structure. Since the carbon (C-25) forming the epoxide linkage with C-3 is β oriented, the ethoxy group was given an α -disposition. In the light of these observations, the structure of **4** has been established as 3,25-epoxy-3 α -ethoxy-olean-12-en-28-oic acid.

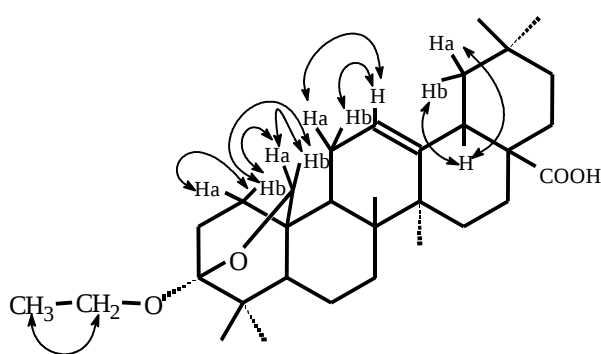


Figure 5. Significant ¹H,¹H COSY Interactions of Lancamaric Acid (**4**)

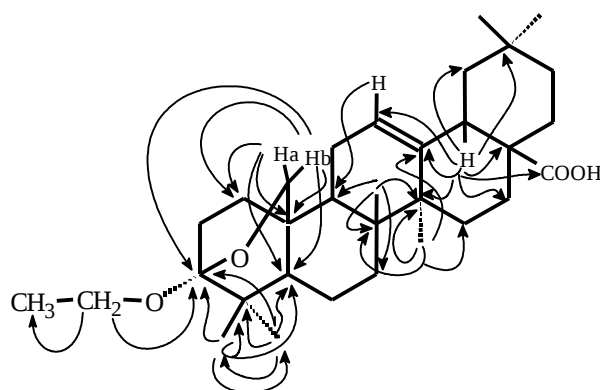


Figure 6. Significant HMBC Interactions of Lancamaric Acid (**4**)

The known compounds (**2**) and (**3**) have been identified through comparison of their spectral data with those of the corresponding constituents reported in literature.^{11,18} However, the ¹H-NMR (at 500 MHz) and ¹³C-NMR (at 125 MHz) assignments of **2** are reported for the first time. The ¹³C-NMR assignments are based on comparison with published values of its methyl ester.¹⁹ Moreover, it is important to note in this context that in the reported²⁰ ¹H-NMR data of **3** assignment of seven three-proton methyl singlets have been made instead of five singlets and two doublets of secondary methyls. In the same reference,

¹³C-NMR data shows twenty eight carbons instead of thirty carbons without exact assignments. It has been reported that **2** and **3** inhibit the growth of mouse melanoma cells in cultures²¹ and *Herpes simplex* virus type I and II *in vitro*.^{20,22}

Table 2. ¹H- and ¹³C- NMR Spectral Data of Compound (**4**) (CDCl₃).

	δ _C	DEPT	δ _H	m	<i>J</i> (Hz)		δ _C	DEPT	δ _H	m	<i>J</i> (Hz)
1	34.6	CH ₂	2.10 (1a) 1.20 (1b)	m	-	17	46.5	C	-	-	-
2	27.7	CH ₂	1.40 (2a) 1.20 (2b)	m	-	18	41.1	CH	2.81	dd	13.8, 4.4
3	100.4	C	-	-	-	19	45.9	CH ₂	1.60 (19a) 1.15 (19b)	m m	- -
4	38.5	C	-	-	-	20	30.6	C	-	-	-
5	50.9	CH	1.15	m	-	21	33.8	CH ₂	1.24	m	-
6	19.6	CH ₂	1.48	m	-	22	32.5	CH ₂	1.23	m	-
7	30.7	CH ₂	1.37	m	-	23	27.3	CH ₃	1.01	s	-
8	40.2	C	-	-	-	24	17.7	CH ₃	0.94	s	-
9	41.8	CH	1.72	m	-	25	67.8	CH ₂	4.26 (25a) 3.86 (25b)	dd dd	8.4, 2.3 8.4, 1.1
10	35.1	C	-	-	-	26	18.4	CH ₃	0.74	s	-
11	23.4	CH ₂	2.00 1.76	- -	- -	27	25.9	CH ₃	1.06	s	-
12	122.6	CH	5.27	t	3.5	28	181.0	C	-	-	-
13	143.6	C	-	-	-	29	33.0	CH ₃	0.88	s	-
14	42.0	C	-	-	-	30	23.6	CH ₃	1.09	s	-
15	27.7	CH ₂	1.05 (15a) 0.90 (15b)	m m	- -	1'	65.0	CH ₂	3.71	q	7.0
16	23.8	CH ₂	1.86	m	-	2'	15.0	CH ₃	1.00	t	7.0

Assignments are based on ¹H, ¹H COSY, NOESY, *J*-resolved, HMQC and HMBC experiments.

EXPERIMENTAL

Melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. UV and IR spectra were recorded on Hitachi-U-3200 and JASCO A-302 spectrometers, respectively. MS spectra were recorded with Finnigan MAT 112 and 312 double focusing mass spectrometers connected to a PDP 11/34 computer system. ¹H- and ¹³C-NMR were measured with a Bruker AM-500 FT-NMR spectrometer operating at 500 MHz for ¹H-NMR and 125 MHz for ¹³C-NMR. The spectra were referenced to the residual solvent signals. The chemical shifts are reported in δ (ppm) and the coupling constants (*J*) are in Hz. For vacuum liquid chromatography (VLC) and flash column chromatography (FCC) silica gel PF₂₅₄ (E. Merck) and silica gel 9385 (E. Merck) respectively were used, while for TLC and preparative TLC silica gel PF₂₄₅ (E. Merck) was used. Hexane used was of the boiling range 60-80°C.

Plant material: Aerial parts of *Lantana 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.

Extraction and Isolation: Air dried aerial parts of *Lantana camara* (10 kg) were extracted with MeOH (20 L) thrice at rt for 48 h. The concentrated extract (1.35 kg), obtained on removal of the solvent from the combined extracts under reduced pressure, was taken in H₂O (5 L) and extracted with EtOAc (15 L) successively. The EtOAc phase gave acidic and neutral fractions on treatment with 4% aqueous Na₂CO₃ and usual work-up. The neutral fraction (129 g) was divided into hexane-soluble and hexane-insoluble

fractions. The hexane-insoluble fraction (66 g) was again divided into Et₂O-soluble and Et₂O-insoluble portions. The Et₂O-soluble fraction (17.5 g) was again divided into hexane soluble and hexane insoluble portions. The residue (3.4 g) obtained from this hexane soluble portion on removal of the solvent, was subjected to VLC (hexane and hexane-EtOAc, in order of increasing polarity) which furnished 7 fractions (Fr-1 to Fr-7). The residue (1.2 g) obtained from the main fraction Fr-2 (hexane-EtOAc 9.5:0.5 eluate) was subjected to FCC (hexane and hexane-EtOAc, in order of increasing polarity) which furnished 12 fractions (Fr-2-1 to Fr-2-12). Fr-2-2 obtained on elution with hexane-EtOAc (9.5:0.5) afforded pure camarolide (**1**) (16 mg) as colorless crystals. Fr-2-5 also obtained on elution with hexane-EtOAc (9.5:0.5) yielded oleanonic acid (**2**) (11.5 mg) as colorless crystals. Fr-2-7 (hexane-EtOAc 9:1 eluate) afforded ursonic acid (**3**) (9.6 mg) as colorless crystals.

The residue (40 g) obtained from the ether insoluble fraction, was subjected to VLC (CHCl₃ and CHCl₃-MeOH in order of increasing polarity) which furnished 9 fractions (Fr-1 to Fr-9). The residue (26 g) obtained from Fr-1 (CHCl₃ and CHCl₃-MeOH 9.9:0.1 eluate) was further subjected to VLC (hexane and hexane-EtOAc, in order of increasing polarity) which furnished 8 fractions (Fr-I to Fr-VIII). The residue (2.6 g) obtained from Fr-II (hexane-EtOAc 8:2 eluate) was subjected to FCC (hexane and hexane-EtOAc, in order of increasing polarity) which furnished 18 fractions (Fr-II-1 to Fr-II-18). Fr-II-10 obtained on elution with hexane-EtOAc (9:1) afforded pure lancamaric acid (**4**) (12.1 mg) as colorless crystals.

Camarolide (1): Colorless needles, mp 204-205 °C (MeOH). UV $\lambda_{\max}$ (MeOH) nm: 210; IR $\nu_{\max}$ (KBr) cm⁻¹: 2920, 2850 (CH), 1755 (lactone C=O), 1700 (ketone C=O), 1620 (C=C) and 1130 (C-O). EI-MS m/z (rel. int., %) 452 (M⁺, 78), 408 (100), 391 (17), 285 (20), 246 (10), 205 (32), 202 (27), 133 (37), 69 (55); HREIMS m/z : 452.3298, (calcd for C₃₀H₄₄O₃, 452.3290), 408.3367 (C₂₉H₄₄O), 285.1930 (C₁₉H₂₅O₂), 205.1588 (C₁₄H₂₁O), 202.1658 (C₁₅H₂₂), 133.1015 (C₁₀H₁₃), 69.0687 (C₅H₉); ¹H- and ¹³C-NMR data: see Table 1.

Oleanonic acid (2): ¹H-NMR (CDCl₃, δ): 5.27 (1H, t, J =3.5 Hz, H-12), 2.80 (1H, dd, J =14.0, 4.5 Hz, H-18), 2.52 (1H, m, H-2a), 2.35 (1H, m, H-2b), 1.11 (3H, s, CH₃), 1.06 (3H, s, CH₃), 1.02 (3H, s, CH₃), 0.99 (3H, s, CH₃), 0.90 (3H, s, CH₃), 0.87 (3H, s, CH₃), 0.79 (3H, s, CH₃); ¹³C-NMR (CDCl₃, δ): 39.1 (C-1), 34.1 (C-2), 217.7 (C-3), 47.4 (C-4), 55.3 (C-5), 19.6 (C-6), 32.2 (C-7), 39.5 (C-8), 46.9 (C-9), 36.8 (C-10), 22.9 (C-11), 122.3 (C-12), 143.6 (C-13), 41.7 (C-14), 27.7 (C-15), 23.5 (C-16), 46.6 (C-17), 41.0 (C-18), 45.8 (C-19), 30.5 (C-20), 33.8 (C-21), 32.2 (C-22), 26.5 (C-23), 21.4 (C-24), 15.0 (C-25), 16.9 (C-26), 25.8 (C-27), 184.1 (C-28), 33.0 (C-29), 23.6 (C-30).

Lancamaric acid (4): Colorless needles, mp 189-190 °C (MeOH). UV $\lambda_{\max}$ (MeOH) nm: 205; IR $\nu_{\max}$ (KBr) cm⁻¹: 3450-2650 (br, COOH), 2920, 2810 (CH), 1700 (acid C=O) and 1620 (C=C). EI-MS m/z (rel. int., %) 498 (M⁺, 12), 453 (6), 452 (10), 248 (100), 205 (8), 203 (45), 133 (22), 119 (16); HREIMS m/z : 498.3701, (calcd for C₃₂H₅₀O₄, 498.3708), 453.3409 (C₃₀H₄₅O₃), 249.1816 (C₁₆H₂₅O₂), 248.1794 (C₁₆H₂₄O₂), 233.1476 (C₁₅H₂₁O₂), 205.1584 (C₁₄H₂₁O), 203.1786 (C₁₅H₂₃), 219.1454 (C₁₄H₁₉O₂), 187.1427 (C₁₄H₁₉), 133.1011 (C₁₀H₁₃), 119.0807 (C₉H₁₁); ¹H- and ¹³C-NMR data: see Table 2.

Methylation of 4: Compound (**4**) formed **4a** as a colorless crystalline substance on treatment with an ethereal solution of diazomethane in cold and keeping the reaction mixture at rt overnight followed by the usual work up: colorless needles, mp 124-125 °C (MeOH). UV $\lambda_{\max}$ (MeOH) nm: 205; IR $\nu_{\max}$ (KBr) cm⁻¹: 2940, 2840 (CH), 1730 (ester C=O) and 1620 (C=C). EI-MS m/z (rel. int., %) 512 (M⁺, 13), 453 (8), 452 (9), 262 (100), 205 (6), 203 (43), 133 (20), 119 (18); HREIMS m/z : 512.3861 (calcd for C₃₃H₅₂O₄, 512.3865), 453.3410 (C₃₀H₄₅O₃), 249.1815 (C₁₆H₂₅O₂), 262.1932 (C₁₇H₂₆O₂), 233.1478 (C₁₅H₂₁O₂), 205.1585 (C₁₄H₂₁O), 203.1788 (C₁₅H₂₃), 219.1456 (C₁₄H₁₉O₂), 187.1429 (C₁₄H₁₉), 133.0998 (C₁₀H₁₃), 119.0807 (C₉H₁₁); ¹H-NMR (CDCl₃, δ): 5.26 (1H, t, J = 3.4 Hz, H-12), 4.25 (1H, dd, J = 8.3, 2.4 Hz, H-25a), 3.87 (1H, dd, J =8.3, 1.0 Hz, H-25b), 3.70 (2H, q, J = 7.0 Hz, H-1'), 2.80 (1H, dd, J = 14.0, 4.4 Hz, H-18), 1.08 (3H, s, CH₃), 1.05 (3H, s, CH₃), 1.02 (3H, s, CH₃), 1.10 (3H, t, J = 7.0 Hz, H-2'), 0.93 (3H, s, CH₃), 0.87 (3H, s, CH₃), 0.75 (3H, s, CH₃).

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