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A TETRACYCLIC DITERPENE AND TRITERPENES FROM *EUPHORBIA SEGETALIS*

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Key Word Index—*Euphorbia segetalis*; Euphorbiaceae; tetracyclic diterpene; segetalol; pentacyclic triterpenes; tetracyclic triterpenes.

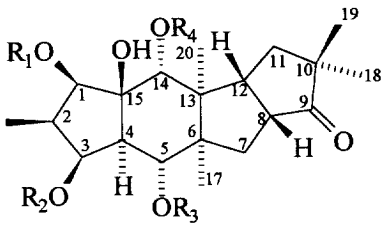
Abstract—A new tetracyclic diterpene, with a novel carbon skeleton, has been isolated from the acetone extract of the whole plant of *Euphorbia segetalis*. Seven known compounds were also isolated: the pentacyclic triterpenes friedeline, lupenone, and glutinol, the tetracyclic triterpenes dammaradienol, cycloartenol and 24-methylenecycloartanol and β-sitosterol. The structure of the new compound and its derivatives have been extensively characterised by high-field NMR spectroscopic methods including 2D NMR techniques.

INTRODUCTION

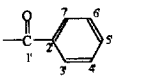
Euphorbia segetalis L. (Euphorbiaceae) is a herb commonly encountered in Portugal. It produces a large amount of latex which causes severe irritation of the skin and eyes during collection. *Euphorbia* species have afforded a large number of polyfunctional diterpenoids with the tigliane, ingenane and daphnane skeletons [1, 2]. Most of them are skin irritants and many of them are skin tumour promoters. Non-irritant polyfunctional macrocyclic diterpenoids, with the lathyrane and jatrophane skeletons, have also been isolated from *Euphorbia* species. Some of these compounds have shown antitumor activity [3, 4]. They are considered biogenetic precursors of the irritants [5]. In continuation of our research on *Euphorbia* species [6–14] we have isolated, from the non-saponifiable part of the acetone extract of the whole plant, a hitherto unknown polyfunctional tetracyclic diterpene parent alcohol (**1b**). The known compounds **2–8** were also isolated. The chemical constituents of the latex of *Euphorbia segetalis* have been investigated and the presence of the compounds **6–8** have also been reported [15].

RESULTS AND DISCUSSION

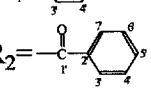
Acetone extract of *Euphorbia segetalis* L. (whole plant) was saponified and the non-saponifiable part was chromatographed on a silica gel column. A further fractionation of the less polar fractions yielded the known pentacyclic triterpenes friedeline (**2**), lupenone (**3**), and glutinol (**4**), and the tetracyclic triterpenes dammaradienol (**5**), cycloartenol (**6**) and 24-methylenecycloartanol (**7**) and β-sitosterol (**8**) identified by their physical and spectroscopic data. Acetylation of one of the more polar fractions afforded a tetraester derivative (**1**) of a polyfunctional diterpene alcohol with a novel tetracyclic diterpene skeleton, named as segetalol (**1b**), which seems to be derived from rearrangement of the bicyclic jatrophane skeleton since the cyclopropane ring, present in the lathyrane skeleton, is absent.



1 R_1=R_3=R_4=Ac; R_2=



1a R_1=R_4=H; R_3= Ac; R_2=



1b R_1=R_2=R_3=R_4=H

The tetraester derivative of segetalol (**1**; 1,5,14-triacetate-3-benzoate) was obtained as crystals (EtOAc–

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Table 1. ^{1}H NMR spectral data of compounds **1**, **1a** and **1b*** (in $CDCl_3$, 300 MHz)

H	**1**	**1a**	**1b**
1α	5.04 *d* (10.2)	4.53 *m* ($W_{1/2}$ 20.0)	4.33 *d* (10.2)
2α	2.88 *m* ($W_{1/2}$ 25.0)	2.65 *m* ($W_{1/2}$ 25.0)	2.35 *m* ($W_{1/2}$ 25.0)
3α	5.80 *dd* (5.4, 6.9)	5.81 *dd* (4.5, 6.3)	4.21 *dd* (4.2, 6.0)
4α	2.40 *dd* (5.1, 12.0)	2.48 *dd* (4.5, 12.0)	1.87 *dd* (4.0, 11.5)
5β	5.68 *d* (12.0)	5.57 *d* (11.7)	4.07 *d* (11.7)
7α	1.48 *dd* (6.9, 14.1)	1.47 *dd* (6.9, 14.1)	1.49 *dd* (6.6, 13.8)
7β	1.82 *dd* (10.5, 14.1)	1.82 *dd* (10.5, 14.1)	2.27 *dd* (10.5, 14.0)
8β	3.23 *m* ($W_{1/2}$ 29.5)	3.17 *m* ($W_{1/2}$ 29.5)	3.07 *m* ($W_{1/2}$ 29.5)
11α	1.78 *dd* (4.5, 14.0)	1.72 *dd* (4.5, 14.0)	1.72 *dd* (4.5, 14.0)
11β	1.96 *dd* (10.2, 14.0)	1.89 *dd* (10.2, 14.0)	1.82 *dd* (10.2, 14.0)
12β	4.22 *m* ($W_{1/2}$ 27.0)	4.11 *m* ($W_{1/2}$ 27.0)	4.02 *m* ($W_{1/2}$ 27.0)
14β	4.83 *s*	3.31 *s*	3.17 *s*
16β-CH_3	0.84 *d* (7.5)	0.97 *d* (7.5)	1.02 *d* (7.5)
17α-CH_3	1.08 *s*	1.10 *s*	1.08 *s*
18α-CH_3	1.06 *s*	1.07 *s*	1.01 *s*
19β-CH_3	1.15 *s*	1.13 *s*	1.11 *s*
20α-CH_3	0.60 *s*	0.79 *s*	0.74 *s*
15-OH†	2.80 *s*	3.47 *s*	—
OH	—	2.28 *brs*	—
OH	—	2.80 *brs*	—
Benzoyl moiety			—
3′	8.02 *brd* (7.2)	7.94 *brd* (7.2)	—
4′	7.46 *brt* (7.8)	7.39 *brt* (7.8)	—
5′	7.58 *brt* (7.5)	7.60 *brt* (7.5)	—
6′	7.46 *brt* (7.8)	7.39 *brt* (7.8)	—
7′	8.02 *brd* (7.2)	7.94 *brd* (7.2)	—
Acetyl moieties			—
R_1	2.14 *s*	—	—
R_3	1.94 *s*	2.01 *s*	—
R_4	2.10 *s*	—	—

* In $CDCl_3/CD_3OD$, 9 : 1.

† Hydroxyl protons were not observed for **1b**; Exchangeable with the solvent.

n-hexane). Its molecular formula was assigned as $C_{33}H_{42}O_{10}$ by LD-FTICR mass spectrometry with the ion at *m/z* 621.26645 $[M+Na]^+$. The IR spectrum of compound **1** exhibited the characteristic absorptions of an hydroxyl group (3455 cm^{-1}), carbonyl groups (1743 ester carbonyl; 1706 cm^{-1} ketone) and an aromatic ring (1469, 778 and 714 cm^{-1}). The EI mass spectrum of **1**, with a molecular ion peak at *m/z* 598, showed a base peak at *m/z* 356 $[M-2\times HOAc-C_6H_5CO_2H]^+$ and fragment peaks at *m/z* 296 $[M-3\times HOAc-C_6H_5CO_2H]^+$, 105 $[C_6H_5CO]^+$ and 77 $[C_6H_5]^+$ indicated the presence of the benzoyl moiety and the three acetoxyl groups which was supported by its ^{1}H NMR and ^{13}C NMR spectra (see Tables 1 and 2). Apart from the signals of the ester groups, the ^{1}H NMR spectrum of **1** showed signals for a secondary methyl group (δ 0.84, *d*, $J = 7.5$ Hz) and four tertiary methyl groups (δ 0.60, 1.15, 1.06 and 1.08) as well as four protons geminal to ester functions (δ 5.04, *d*; 5.80, *dd*; 5.68 *d*; 4.83, *s*). A singlet at δ 2.80, which disappeared with D_2O, revealed an hydroxyl group which was not acetylated indicating its tertiary nature. In addition to the signals of the ester groups, the ^{13}C and DEPT NMR spectra of **1** showed signals of 20 carbon atoms corresponding to five CH_3, two CH_2, eight CH (four oxymethines), and five quaternary carbons (a carbonyl group at δ 224.7 and a C—OH at δ 82.6). Among the 20 carbons, there were no sp^2 carbon atoms indicating the saturated nature of **1**. Based on the thirteen degrees of unsaturation given by the molecular formula ($C_{33}H_{42}O_{10}$), a tetracyclic diterpenoid skeleton ($C_{20}H_{32}O_6$) was proposed for **1**.

The COSY (^{1}H–^{1}H correlation) and HETCOR (^{1}H–^{13}C correlation) experiments of **1** led to the establishment of the structure of three main fragments, separated by quaternary carbons: $CH(OR_1)$—CH (CH_3)—$CH(OR_2)$—CH—$CH(OR_3)$, CH_2—CH—CH —CH_2 and $CH(OR_4)$. The quaternary carbons bridging these fragments were assigned by analysis of the ^{1}H–^{13}C two and three bond correlations of the HMBC spectrum of **1**. The hydroxylic carbon C-15 is correlated with the oxymethine protons H-3 (δ 5.80) and H-14 (δ 4.83) and with H-2 (δ 2.88) and H-4 (δ 2.40). The downfield shift of the carbonyl resonance at δ 224.7 suggested the presence of a methyl-substituted five membered ring ketone [16] which agrees with the correlations of this carbon with the protons H-8 (δ 3.23) and H-12 (δ 4.22) and with the geminal methyl

Table 2. ^{13}C NMR spectral data of compounds **1**, **1a**, **1b*** (in $CDCl_3$, 75.4 MHz)

C	1	1a	1b	DEPT
1	74.6	72.8	72.6	CH
2	37.8	39.4	39.5	CH
3	73.0	75.7	74.2	CH
4	43.2	42.3	43.6	CH
5	68.6	69.1	67.5	CH
6	53.2	53.2	53.0	C
7	35.4	35.6	35.7	CH_2
8	46.4	46.5	46.8	CH
9	224.7	225.0	226.8	C
10	47.0	47.1	47.1	C
11	35.6	35.7	35.5	CH_2
12	40.7	40.6	40.5	CH
13	51.9	51.3	51.8	C
14	72.2	71.2	70.9	CH
15	82.6	85.0	85.0	C
16	10.2	9.6	9.3	CH_3
17	16.4	16.7	16.3	CH_3
18	22.8	22.9	22.7	CH_3
19	29.4	29.4	29.7	CH_3
20	15.3	16.2	15.5	CH_3
Benzoyl moiety†				
1′	166.1	165.6	—	CO
2′	129.7	129.4	—	C
3′/7′	128.5	128.6	—	CH
4′/6′	129.7	129.6	—	CH
5′	133.2	133.3	—	CH
Acetyl moieties†				
R_1	169.9		—	CO
	20.6		—	CH3
R_3	170.6	170.9	—	CO
	20.9	21.0	—	CH_3
R_4	169.7	—	—	CO
	20.8	—	—	CH_3

*In $CDCl_3/CD_3OD$, 9 : 1.
†See structures **1**–**1b**

groups at C-10 (δ 1.06 and 1.15). Similarly, correlations of the quaternary carbon C-13 with H-12, H-8 and Me-17 (δ 1.08), and of C-6 with the protons geminal to the ester functions H-14 and H-5 (δ 5.68) and Me-20 (δ 0.60) indicated the presence of the inner five membered ring.

The after mentioned 2D long range ^1H–^{13}C chemical shift correlation also led to the location of the four ester functions. The ester carbonyl carbon at δ 166.1 correlates with the aromatic protons at δ 8.02 and with H-3 indicating that it is attached to C-3 and to the aromatic ring. The ester carbonyl at δ 169.7 is bound to C-14 since it correlates with H-14 and the methyl at δ 2.10. Similarly, the carbonyl at δ 169.9 correlates with H-1 and the methyl at δ 2.14 and is attached to C-1. The remaining ester carbonyl carbon resonance at δ 170.6 correlates with H-5 and with the methyl at δ 1.94 and therefore is bound to C-5.

The coupling constants of the protons H-1, H-3, H-4 and H-5, in compound **1**, were similar to those reported for euphoratines A, B and C [17] and euphactins A and C [18]. Thus, the configuration at C-2 to C-5 and C-15 must be identical to that of these model compounds. However, it differed from that of euphoractines D and E [17] and from euphactins B and D [18] with an α-methyl group at C-2. The relative configuration of these chiral centres of **1** was confirmed by a NOESY spectrum. The enhancements observed in this spectrum also led to the stereochemistry of the remaining carbons. The strong NOE enhancements of H-4 at H-3 and H-1 confirm that they are located on the same side of the molecule. Furthermore, the enhancement of H-4 at Me-17 indicates that both lies also on the same face. The hydroxyl group at C-15 has also the same β-orientation as the functional group at C-3 since the hydroxylic proton is correlated with Me-16. The strong NOE cross peaks between the vicinal methine protons H-8 and H-12 show that they have the same β-configuration as opposed to the methyl groups at C-13 and C-6 which show the α-configuration. This relationship is derived from the absence of NOE correlations between these two methines and Me-17 and Me-20. In addition, H-8 is also correlated with the oxygen-bearing methines H-5, H-14 and Me-19, which allocates these groups on the β-face of **1**. Figure 1 illustrates the most relevant NOE correlations used to establish the stereochemistry of **1**.

Alkaline hydrolysis of **1**, with 0.1 M potassium hydroxide-methanol, at room temperature, yielded the parent alcohol **1b** and the partially hydrolysed diester derivative **1a** (5-acetate-3-benzoate). The molecular formula of **1a** was assigned as $C_{29}H_{38}O_8$ by LD-FTICR mass spectrometry with the ion at m/z 553.18872 $[M+K]^+$. The EI mass spectrum of **1b**, the parent alcohol, showed a molecular ion peak at m/z 368 indicating a molecular formula of $C_{20}H_{32}O_6$. Compounds **1a** and **1b** gave essentially the same ^1H NMR and ^{13}C NMR spectra as **1** except for the chemical shifts of carbons and protons which are dependent of the functional groups. The ^1H NMR and ^{13}C NMR spectra of **1a** showed the removal of two acetoxyl groups from **1**. The doublet at δ 5.04 (δ 74.6) and the singlet at δ 4.83 (δ 72.2) were diamagnetically shifted to δ 4.53 (δ 72.8) and to δ 3.31 (δ 71.2), respectively, and the acetyl methyl singlets at δ 2.14 (δ 169.9 and

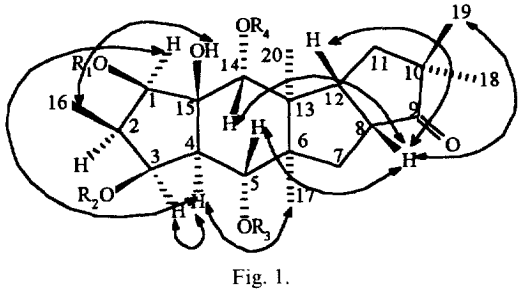

Fig. 1.

20.6) and δ 2.10 (169.7 and 20.8) disappeared. In addition, the signals of Me-16 and Me-20 were paramagnetically shifted to δ 0.97 and to δ 0.79; this was due to the deshielding effect of the hydroxyl groups at C-1 and at C-14 on Me-16 and Me-20, respectively. The ^{1}H NMR and ^{13}C NMR spectra of **1b**, the parent alcohol, revealed the hydrolysis of the remaining ester groups of **1**, the benzoyl group at C-3 and the acetoxyl group at C-5. The signal of H-4 was diamagentically shifted to δ 1.87 ($\Delta\delta = -0.59$ ppm) owing to the deshielding effect of the benzene ring in H-4 of **1** and **1a**. The signal of H-7β appeared shifted downfield. The other proton resonances of **1b** remained practically unchanged.

EXPERIMENTAL

General

Mps uncorr.; IR: KBr or film; ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz), Varian Unity-300 NMR spectrometer, $CDCl_3$, TMS as int. standard; MS: Kratos MS25RF (70 eV) and Finnigan-FT-2001 for LD-FTICR-MS.

Plant material

The plant material was collected at Leiria, Portugal, and identified by Dr. Teresa Vasconcelos from the Department of Botany and Biologic Engineering of Instituto Superior de Agronomia, University of Lisbon. A voucher specimen has been deposited at the Herbarium (LISI) of Instituto Superior de Agronomia.

Extraction and isolation

The air dried whole plant (2.1 kg) was extracted with Me_2CO (4 × 10 l) at room temp. for 4 days. Each extract was filtered on a Buchner funnel and evaporated under red. pres. at low temp. (40°). The combined extracts gave a residue of 180 g.

Saponification

A 10% KOH soln. in MeOH (1 l) was added to the total extract. The mixture was left at room temp. for 36 h. After concentration of the MeOH, at red. pres. the residue was suspended in 1 l of H_2O and extracted several times with Et_2O. The combined extracts, containing the non-saponifiable part, were dried (Na_2SO_4) and evaporated, yielding a residue of 110 g. The non-saponifiable part was then dissolved in hot Me_2CO and cooled. The ppt. was filtered off (6 g of Me_2CO insoluble part). The filtrate was evaporated giving 104 g of Me_2CO soluble part.

Separation of the above-mentioned extract (104 g, Me_2CO soluble part) was performed by CC on silica gel (1 kg) with *n*-hexane–EtOAc mixtures of increasing polarity. Repeated chromatography of the less polar frs on silica gel or $AgNO_3$–silica gel (1:9; 2:8) and crystallisation (M_2CO–MeOH) afforded **2** (4 mg; *n*-hexane–EtOAc, 19:1), **3** (60 mg; *n*-hexane–EtOAc, 19:1), **4** (9 mg; *n*-hexane–EtOAc, 9:1), **5** (70 mg; *n*-hexane–EtOAc, 7:1) **6** (600 mg; *n*-hexane–EtOAc, 7:1), **7** (120 mg; *n*-hexane–EtOAc, 7:1), **8** (200 mg; *n*-hexane–EtOAc, 3:1).

The fraction eluted with *n*-hexane–EtOAc (1:1) was acetylated with Ac_2O–pyridine (1:1) at room temp. overnight. The usual workup gave a residue which was chromatographed twice on silica gel columns with *n*-hexane–EtOAc and CH_2Cl_2–EtOAc mixtures yielding 200 mg of **1** (CH_2Cl_2–EtOAc, 9:1).

Segetalol-1,5,14-triacetate-3-benzoate (**1**). Mp 151–153° (EtOAc-*n*-hexane); $[\alpha]_D^{20}$ −59.66° ($CHCl_3$; *c* 0.30); LD-FTICR-MS *m/z* 621.26645 $[M+Na]^+$ ($C_{33}H_{42}O_{10}Na$ requires 621.26702); IR ν_{max}^{KBr} cm^{-1} 3455, 2987, 2895, 1743, 1706, 1469, 1383, 1283, 1232, 1123, 1031, 778, 714. ^{1}H NMR and ^{13}C NMR: see Tables 1 and 2; EIMS (probe) 70 eV, *m/z* (rel. int): 598 $[M]^+$ (1), 580 $[M-H_2O]^+$ (0.5), 538 $[M-HOAc]^+$ (18), 523 $[M-HOAc-CH_3]^+$ (12), 478 $[M-2\times HOAc]^+$ (33), 460 $[M-2\times HOAc-H_2O]^+$ (5), 418 (13), 415 (31), 373 (15), 356 $[M-2\times HOAc-C_6H_5CO_2H]^+$ (100), 341 $[M-2\times HOAc-C_6H_5CO_2H-CH_3]^+$ (11), 338 $[M-2\times HOAc-C_6H_5CO_2H-H_2O]^+$ (19), 331 (11), 314 (55), 304 (14), 299 (1), (10), 296 $[M-3\times HOAc-C_6H_5CO_2H]^+$ (67), 281 (42), 278 (27), 238 (68), 210 (30), 189 (25), 158 (25), 134 (55), 105 $[C_6H_5CO]^+$ (73), 91 (78), 77 (63).

Alkaline hydrolysis of compound **1**

Compound **1** (25 mg) was treated with 0.1 M KOH in MeOH (4 ml) at room temp. for 3 h. After concentration, the residue was suspended in 2 ml of H_2O and extracted with EtOAc (4 × 5 ml). The combined extracts were dried (Na_2SO_4) and evaporated, yielding a residue of 15 mg. After prep. TLC (CH_2Cl_2–EtOAc, 3:1) 10 mg of **1a** and 4 mg of **1b** were obtained.

Segetalol-5-acetate-3-benzoate (**1a**). Gum $[\alpha]_D^{20}$ −37.50° ($CHCl_3$; *c* 0.19); IR ν_{max}^{film} cm^{-1}: 3437, 2973, 2929, 1717, 1470, 1382, 1281, 1232, 1116, 1026, 714. ^{1}H NMR and ^{13}C NMR: see Tables 1 and 2. LD-FTICR-MS *m/z* (rel. int): 553.18872 $[M+k]^+$ (100) ($C_{29}H_{38}O_8K$ requires 553.35449) 537 $[M+Na]^+$ (9), 449 $[M+Na-HOAc-H_2O]^+$ (7), 429 (6).

Segetalol (**1b**). Mp 294–296° (EtOAc–*n*-hexane); $[\alpha]_D^{20}$ −18.96° (MeOH *c* 0.13); IR ν_{max}^{film} cm^{-1} 3349, 2958, 2915, 1720, 1434, 1383, 1038. ^{1}H NMR and ^{13}C NMR: see Tables 1 and 2. EIMS (probe) 70 eV: *m/z* (rel. int): 368 $[M]^+$ (1), 350 $[M-H_2O]^+$ (8), 332 $[M-2\times H_2O]^+$ (28), 317 $[M-2\times H_2O-CH_3]^+$ (5), 314 $[M-3\times H_2O]^+$ (11), 299 $[M-3\times H_2O-CH_3]^+$ (5), 296 $[M-4\times H_2O]^+$ (3), 291 (63), 285 (10), 281 $[M-4\times H_2O-CH_3]^+$ (3), 263 (11), 245 (13), 226 (9), 220 (9), 190 (38), 172 (100), 154 (67), 125 (30), 102 (67), 95 (56), 55 (52).

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