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Steroids and a tetracyclic diterpene from *Euphorbia boetica*

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Abstract

From the Me_2CO extract of the whole plant of *Euphorbia boetica* a new tetracyclic diterpene was isolated. Its structure was established based on NMR spectroscopic data obtained using a combination of one- and two-dimensional techniques. The known steroids 5α-stigmastane-3β-6α-diol, 5α-stigmastane-3β-5,6β-triol and β-sitosterol glucopyranoside were also isolated.

Keywords: *Euphorbia boetica*; Euphorbiaceae; Tetracyclic diterpene; Eufoboetol; Steroids; 5α-Stigmastane-3β-6α-diol; 5α-Stigmastane-3β-5,6β-triol; β-Sitosterol glucopyranoside

1. Introduction

Euphorbia boetica Boiss. (Euphorbiaceae), an herb endemic to Europe, is widespread in the southern regions of Portugal. It produces a large amount of latex which causes irritation of the human skin. In the framework of our phytochemical research on *Euphorbia* species (Ferreira, Lobo, O'Mahoney, Williams, & Wyler, 1990, 1991; Ferreira, Lobo, & Wyler, 1993a, 1993b; Ferreira, Lobo, Nascimento, & Wyler, 1994; Ferreira, Ascenso, & Tavares, 1995; Tavares, Duarte, Cunha, Ascenso, & Ferreira, 1995; Ferreira, Duarte, & Ascenso, 1996; Ascenso, & Ferreira, 1997; Ferreira, Madureira, & Ascenso, 1998) we have been studied *Euphorbia boetica*. From this species we have reported previously the isolation and structural determination of several tetra and pentacyclic triterpenes (Ferreira et al., 1995; Tavares et al., 1995). We now report herein the isolation and structural determination of a new polyfunctional tetracyclic diterpene parent alcohol **1a**. The known steroids **2**–**4** were also isolated.

2. Results and discussion

Acetone extract of the air-dried whole plant of *Euphorbia boetica* Boiss. was saponified and the non-saponifiable part was subjected to column chromatography on a silica gel column. Repeated chromatography of a few crude fractions yielded several triterpenes (Ferreira et al., 1995; Tavares et al., 1995).

Acetylation of one of the most polar fractions afforded a triester derivative (**1**) of a new polyfunctional tetracyclic diterpene alcohol, named as eufoboetol (**1a**) which seems to be derived from rearrangement of the tricyclic latyrane skeleton and structurally related to myrsinol (Rentzea, Hecker, & Lotter, 1982; Rentzea, & Hecker, 1982). The same basic skeleton was found previously on a few pentacyclic diterpenes isolated from *Euphorbia aleppica* were the presence of a fifth ring is due to a 13,17 ether bridge (Shi, Jia, Jamil, & Sadiq, 1995; Yang, Shi, Jia, Saleh, & Lahham, 1995; Öksüz et al., 1996). The known steroids 5α-stigmastane-3β-6α-diol (**2**) and β-sitosterol glucopyranoside (**4**), as their acetylated derivatives, and 5α-stigmastane-3β-5,6β-triol (**3**) acetylated at C-3 and C-6, were also isolated and identified by their physical and spectroscopic data. ^1H NMR and ^{13}C NMR data of compound **3** are reported herein because they were

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not found in literature for this derivative of 5α-stigmastane-3β-5,6β-triol.

The molecular formula, $C_{26}H_{38}O_{10}$, of the triester derivative (**1**; 3,5,17-triacetate) of the parent alcohol eufoboetol, obtained as crystals (*n*-hexane), was deduced by LD-FTICR-MS mass spectrometry with the ion at *m/z* 533.29138 $[M+Na]^+$. Its IR spectrum showed intense absorptions for hydroxyl groups (3520, 3420 cm^{-1}), carbonyl groups (1745, 1728, 1718 ester carbonyl; 1700 cm^{-1} ketone). The EI mass spectrum of **1**, with a molecular ion peak at *m/z* 510, showed fragment peaks at *m/z* 389 $[M–H_2O–Ac–HOAc]^+$, 329 $[M–H_2O–Ac–2 \times HOAc]^+$ and 269 $[M–H_2O–Ac–3 \times HOAc]^+$ indicating the presence of the three acetoxyl groups which was supported by its ^1H and ^{13}C NMR spectra (see Tables 1 and 2). Apart from the signals of the acetyl groups the ^{13}C and DEPT spectra of **1** revealed that the basic carbon skeleton consisted of 20 carbon atoms corresponding to four CH_3, three CH_2 (one CH_2–O), eight CH (three oxymethines), and five quaternary carbons (a carbonyl group at δ 211.5 and two C–OH at δ 82.8 and 85.5). Among the 20 carbons, there were no sp^2 carbon atoms indicating the saturated nature of **1**. Based on the eight degrees of unsaturation given by the molecular formula ($C_{26}H_{38}O_{10}$), a tetracyclic diterpenoid skeleton ($C_{20}H_{32}O_7$) was proposed for **1**. In addition to the signals of the acetyl groups the ^1H NMR spectrum of **1** showed, in the upfield region, signals of a secondary methyl group (δ 1.01, d, $J=7.2$ Hz), two methyl singlets (δ 0.92 and δ 1.22) and a singlet of a methyl group bonded to an oxygen-bearing carbon atom (δ 2.39). The ^1H NMR spectrum of **1** displayed also two methine protons geminal to ester functions (δ 5.58, dd, $J=4.2$ and 5.4 Hz; 5.44, d, $J=11.7$ Hz) and one oxygenated methylene as an AB system (δ 4.27, d, $J=13.2$ Hz and 4.89, d, $J=13.2$ Hz). D_2O exchange resulted in the disappearance of a broad signal at δ 3.5 and of two singlets at δ 3.15 and δ 4.57 revealing the presence of three hydroxyl groups.

In the ^{13}C NMR spectrum the high-field methine signals at δ 20.1 and δ 18.7 and the quaternary carbon at δ 18.9 with two methyl carbons at δ 28.6 and δ 15.5 indicated the presence of a gem-dimethyl cyclopropane ring (Yang et al., 1995; Shi, & Jia, 1995) which was further supported by the particularly high field protons signals at δ 0.29 (dd, $J=7.8$ and 9.6 Hz) and δ 0.67 (td, $J=1,8$ Hz and 9.6 Hz).

The COSY (^1H–^1H correlation) and HETCOR (^1H–^{13}C correlation) experiments of **1** showed three main

Table 1
^1H NMR chemical shifts for compounds **1** and **1a** (300 MHz). Coupling constants (*J* in Hz) are given in parentheses

H	**1**[a]	**1a**[b]	**1a**[c]
1α	2.29 dd (11.5, 13.5)	2.25 dd (11.5, 13.5)	2.30 dd (11.5, 13.5)
1β	1.07 dd (5.4, 13.5)	1.05 dd (5.5, 13.0)	0.98 dd (5.8, 13.0)
2α	2.40 m	2.19 m	2.20 m
3α	5.58 dd (4.2, 5.4)	4.21 dd (4.2, 5.4)	4.25 dd (4.2, 5.4)
4α	2.75 dd (4.2, 11.7)	2.35 dd (4.2, 11.7)	2.36 dd (4.2, 11.7)
5β	5.44 d (11.7)	4.55 d (11.7)	4.68 d (11.7)
7α	3.83 br d (7.0)	3.98 br d (7.1)	4.15 d (6.3)
7-OH[d]	3.50 br s	–	–
8α	2.11 m	2.11 m	2.11 m
8β	1.76 dt (1.8, 16.2)	1.54 dt (1.8, 16.2)	1.62 dt (1.8, 16.2)
9α	0.67 td (1.8, 9.6)	0.65 td (1.8, 9.6)	0.63 td (1.8, 9.6)
11α	0.29 dd (7.8, 9.6)	0.56 dd (7.8, 9.6)	0.45 dd (7.8, 9.6)
12β	2.83 d (7.8)	2.51 d (7.8)	2.67 d (7.8)
13-OH[d]	4.57 s	–	–
15-OH[d]	3.15 s	–	–
16β-CH_3	1.01 d (7.2)	1.12 d (7.2)	1.10 d (7.2)
17a	4.27 d (13.2)	3.75 d (12.0)	3.80 d (12.0)
17b	4.89 d (13.2)	4.14 d (12.0)	4.30 d (12.0)
18α-CH_3	0.92 s	0.95 s	0.92 s
19β-CH_3	1.22 s	1.07 s	1.15 s
20β-CH_3	2.39 s	2.36 s	2.29
Acetyl moieties			
R_1	2.06 s	–	–
R_2	2.01 s	–	–
R_3	2.03 s	–	–

[a] In $CDCl_3$.
[b] In $CDCl_3/CD_3OD$, 9:1.
[c] In CD_3OD.
[d] Hydroxyl protons were not observed for **1a**; exchangeable with the solvent.

Table 2
^{13}C NMR chemical shifts for compounds **1** and **1a** (75.4 MHz)

C	**1**[a]	**1a**[b]	**1a**[c]	DEPT
1	40.2	40.5	41.7	CH_2
2	35.6	36.8	38.5	CH
3	77.0	75.3	76.4	CH
4	47.9	50.5	51.7	CH
5	69.6	66.4	68.2	CH
6	46.0	46.7	47.6	C
7	63.5	65.3	65.0	CH
8	23.8	25.5	26.6	CH_2
9	20.1	19.1	20.5	CH
10	18.9	18.5	19.4	C
11	18.7	20.4	21.9	CH
12	33.2	34.2	34.5	CH
13	82.8	81.7	84.0	C
14	211.5	216.6	216.0	CO
15	85.5	86.1	86.9	C
16	15.8	15.9	16.3	CH_3
17	63.4	62.0	63.3	CH_2
18	28.6	28.5	29.2	CH_3
19	15.5	15.5	16.3	CH_3
20	27.0	28.1	28.4	CH_3
Acetyl moieties				
R_1	169.2	–	–	CO
	20.7	–	–	CH3
R_2	170.5	–	–	CO
	21.1	–	–	CH_3
R_3	173.1	–	–	CO
	20.8	–	–	CH_3

[a] In $CDCl_3$.
[b] In $CDCl_3/CD_3OD$, 9:1.
[c] In CD_3OD.

partial structures which are separated by quaternary carbons (Figs. 1 and 2). The quaternary carbons bridging these fragments were assigned by analysis of the ^1H–^{13}C two and three bond correlations of the HMBC spectrum of **1**. The carbon C-15 (C–OH), at δ 85.5, is correlated with the oxymethine proton H-5 (δ 5.44), with H-1 at δ 1.07 and H-4 (δ 2.75). The quaternary carbon C-13 (δ 82.8) is correlated with H-12 (δ 2.83) and H-11 (δ 0.29). The carbonyl resonance at δ 211.5 is correlated with the proton of the tertiary hydroxylic group at C-13 (δ 4.57) and with its geminal methyl group at δ 2.39 establishing the location of the ketone carbonyl group at C-14 in ring B. Correlation of C-6 (δ 46.0) with H-4 (δ 2.75), H-8 (δ 1.76), H-12 and with methylene protons at C-17 (δ 4.27 and 4.89), assigned

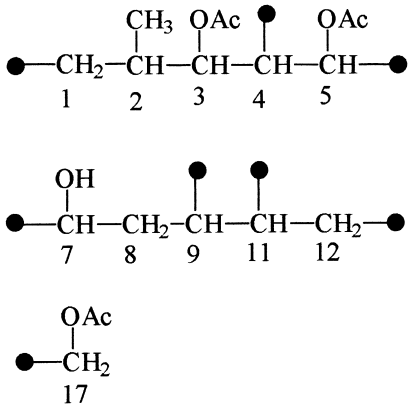

Fig. 1. Partial structures of **1** derived from COSY and HETCOR 2D spectra; • quaternary carbon atoms.

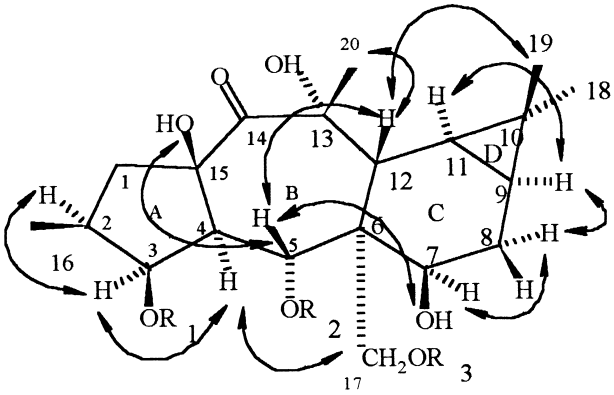

Fig. 2. Relevant NOE correlations observed for **1**.

carbon C-6 at the fusion of ring B and ring C. The attachment of the methylene group C-17 at C-6 was unambiguously indicated not only by the previous correlation of this carbon (δ 46.0) with the methylene protons but also by the correlation of these protons with C-5 (δ 69.6). Correlation of H-11 with the upfield quaternary carbon C-10 resonance at δ 18.9 confirmed the presence of the three member ring, with two geminal methyl groups, attached to ring C.

The HMBC spectrum of **1** showed also the location of each acetyl group. The acetyl carbonyl carbon at δ 169.2 correlates with the methyl protons at δ 2.06 and with H-3 indicating that it is attached to C-3. The acetyl carbonyl at δ 170.5 is bound to C-5 since it correlates with H-5 and the methyl at δ 2.01. The remaining ester carbonyl carbon at 173.1 must be attached to C-17 since it is correlated with the methylene protons at this carbon and the methyl protons at δ 2.03.

The stereochemistry of ring A, namely of H-3 (which was assumed to be α) was taken as reference, based in the similarity of the protons coupling constants of ring A (Table 1) with known model compounds. The proton coupling constants of H-1, H-3, H-4 and H-5, in compound **1**, were similar to those reported for diterpenes structurally related to latyrane skeleton (Shi, & Jia, 1995; Shi, Jia, & Cui, 1995; Wu, Sorg, & Hecker, 1995; Yang et al., 1995). Thus, the configuration at C-2 to C-5 and C-15 must be identical to that of these model compounds. The relative configuration at these chiral centers of **1** was confirmed by a NOESY spectrum, which was also used to derive the stereochemistry of the remaining carbons. Very strong NOE cross peaks from H-3 to H-4 and H-2 indicated that they must lie on the same side of the molecule. H-4 gave also very strong NOE cross peaks with H-3 and with one of the protons of the methylene group at C-17 indicating also an α orientation for this group. The large proton coupling constant observed between H-4 and H-5 ($J_{4,5} = 11.7$ Hz) (Fakunle, Connlly, & Rycroft, 1989) and the existence of strong NOE cross peaks from H-5 to H-12 and to OH-15 requires a *trans* junction between ring A and ring B and a β configuration for H-5. From these results we can also deduce the *trans* fusion of B and C rings.

The very strong NOE cross peak from H-12 to CH_3-19 and the strong NOE effects of H-11 at 17a-H, OH-13, CH_3-18 and H-9 led to the conclusion that ring D is *cis* fused. The strong NOE effect from H-12 at the CH_3-20 group provides further evidence for the configuration at C-13.

In ring C the strong NOE cross peak observed between H-9 and H-8 (δ 2.11) indicates that this proton is H-8α. Similarly the NOE effects from H-7 at H-8α and at H-17a proved that H-7 is α. The correlations of the OH group at C-7 with H-5 assigned the β orientation of the OH group at C-7.

Under basic catalysis an α-ketol rearrangement was reported for compounds related to **1** (Ishiguro, Kondo, & Takemoto, 1975; Rentzea, & Hecker, 1982). With the basic conditions used for saponification of the crude extract this rearrangement did not occur in **1**. The presence of a ketone function at C-14 with a hydroxyl group at C-15 is characteristic of several latyrane-type diterpenes (Rentzea et al., 1982; Öksüz et al., 1995).

Alkaline hydrolysis of **1**, with 0.1 M potassium hydroxide-methanol, at room temp., yielded the parent alcohol **1a**. The molecular formula of **1a** was assigned as $C_{20}H_{32}O_7$ by FABMS mass spectrometry with the ion at m/z 407 $[M+Na]^+$. The ^1H and ^{13}C NMR spectra of **1a** showed the removal of all the acetoxyl groups from **1** which was also indicated by the absence of the absorptions bands of the carbonyl esters in the IR spectra and by the fragmentation patterns in the mass spectrum. The oxymethine protons at δ 5.58 (δ 77.0) and at δ 5.44 (δ 69.6) were diamagnetically shifted to δ 4.21 (δ 75.3) and to δ 4.55 (δ 66.4) respectively and the doublets of the AB system at δ 4.27 and δ 4.89 (δ 63.4) appeared at δ 3.75 and δ 4.14 (δ 62.0). The signals of the acetyl methyl singlets at δ 2.06 (δ 169.2 and 20.7), δ 2.03 (173.1 and 20.8) and δ 2.01 (170.5 and 21.1) were absent.

3. Experimental

3.1. General

Mps uncorr.; IR: KBr or film; ^1H NMR (300 MHz) and ^{13}C NMR (75.4 MHz), Varian Unity-300 NMR spectrometer, $CDCl_3$, CD_3OD, TMS as int. standard; MS: 70 eV Kratos MS25RF and Finnigan-FT-2001 for LD-FTICR-MS.

3.2. Plant material

The plant material was collected at Coruche, 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.

3.3. Extraction and isolation

The air dried whole plant (2.3 kg) was extracted with Me_2CO (4×12 l) at room temp. for three days. Each extract was filtered on a Buchner funnel and evaporated under reduced pressure at low temp. (40°). The combined extracts gave a residue of 164 g.

3.4. 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 reduced pressure, the residue was suspended in 1 l of H_2O and extracted several times with *n*-hexane and ether. The combined extracts (*n*-hexane and ether), containing the non-saponifiable part, were dried (Na_2SO_4) and evaporated, yielding a residue of 40 g. The non-saponifiable part was then dissolved in hot Me_2CO and cooled. The ppt. was filtered off (10 g of Me_2CO insoluble part). The filtrate was evaporated giving 30 g of Me_2CO soluble part.

Separation of the above-mentioned extract (30 g, Me_2CO soluble part) was performed by CC on silica gel (1.3 kg) with *n*-hexane/EtOAc mixtures of increasing polarity.

The fraction eluted with *n*-hexane/EtOAc (1:1–1:9) was acetylated with Ac_2O-pyridine (1:1) at room temp. overnight. The usual workup gave a residue which were chromatographed on silica gel column with *n*-hexane/EtOAc and EtOAc/MeOH mixtures. The fr. hexane/EtOAc (4:1) was submitted to prep. TLC (silica gel GF 254) with *n*-hexane/EtOAc (4:1; 3×) yielding 20 mg of **2**. The fr. hexane/EtOAc (3:1), after prep. TLC (silica gel GF 254) with CH_2Cl_2/EtOAc (9:1) yielded 15 mg of **3**. From the fr. *n*-hexane/EtOAc (7:3) were obtained, after crystallization (Me_2CO/MeOH) 95 mg of **4**. The fr. hexane/EtOAc (3:2) was further purified by prep. TLC, using as developing solvent hexane/EtOAc (7:3; 3×), and crystallization (*n*-hexane) to afford 30 mg of the diterpene **1**.

3.5. Eufoboetol-3,5,17-triacetate (*1*)

Mp 174–175° (*n*-hexane); $[\alpha]_D^{20}$ −18.50° ($CHCl_3$; *c* 0.40); LD-FTICR-MS *m/z* 533.29138 $[M+Na]^+$ ($C_{26}H_{38}O_{10}Na$ requires 533.56943); IR *ν* max KBr 3520, 3420, 2928, 1700, 1718, 1728, 1745, 1440, 1385, 1260, 1245, 1230, 1045, 1020 cm^{-1}; ^1H and ^{13}C NMR (see Tables 1 and 2); EIMS (probe) 70 eV, *m/z* (rel. int): 510 $[M]^+$ (1), 492 $[M–H_2O]^+$ (1), 467 $[M–Ac]^+$ (3), 449 $[M–H_2O–Ac]^+$ (34), 407 $[M–Ac–HOAc]^+$ (4), 389 $[M–H_2O–Ac–HOAc]^+$ (20), 347 $[M–Ac–2\times HOAc]^+$ (5), 329 $[M–H_2O–Ac–2\times HOAc]^+$ (35), 311 $[M–2\times H_2O–Ac–2\times HOAc]^+$ (6), 287 $[M–Ac–3\times HOAc]^+$ (11), 269 $[M–H_2O–Ac–3\times HOAc]^+$ (23), 251 $[M–2\times H_2O–Ac–3\times HOAc]^+$ (13), 241 (9), 239 (8), 43 $[Ac]^+$ (100).

3.6. Alkaline hydrolyse of compound *1*

Compound **1** (15 mg) was treated with 0.1 M KOH in MeOH (3 ml) at room temp. for 6 hr. After concentration the MeOH, the residue was suspended in 2 ml of H_2O and extracted with EtOAc (4×4 ml). The combined extracts were dried (Na_2SO_4) and evaporated, yielding 9 mg of **1a**.

3.7. Eufoboetol (*1a*)

Gum; IR ν_{max} film 3420, 3340, 2928, 2856, 1690, 1460, 1385, 1170, 1060, 1004 cm^{-1}; ^1H and ^{13}C NMR (see Tables 1 and 2); FABMS, *m/z* (rel. int): 407 $[M+Na]^+$ (7), 385 $[M+H]^+$ (2), 367 $[M+H–H_2O]^+$ (3), 349 $[M+H–2\times H_2O]^+$ (4), 337 (4), 331 $[M+H–3\times H_2O]^+$ (8), 313 $[M+H–4\times H_2O]^+$ (5), 55 (100).

3.8. α-stigmastane-3β-5,6β-triol 3,6 diacetate (*3*)

^1H (300 MHz, $CDCl_3$): δ 0.68 (3H, s, H-18), 0.81 (3H, d, $J=6.6$ Hz, H-27), 0.83 (3H, d, $J=6.6$ Hz, H-26), 0.84 (3H, t, $J=7.2$ Hz, H-29), 0.91 (3H, d, $J=6.6$ Hz, H-21), 1.15 (3H, s, H-19), 2.02, (3H, s, OAc), 2.07 (3H, s, OAc), 4.69 (1H, br s, H-6α), 5.14 (1H, m, $W_{1/2}=25$ Hz, H-3α); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 31.8 (C-1), 26.6 (C-2), 70.6 (C-3), 36.8 (C-4), 75.0 (C-5), 76.2 (C-6), 31.4 (C-7), 30.7 (C-8), 45.1 (C-9), 38.45 (C-10), 21.04 (C-11), 39.8 (C-12), 42.7 (C-13), 55.7 (C-14), 24.1 (C-15), 28.2 (C-16), 56.1 (C-17), 12.0 (C-18), 16.4 (C-19), 36.2 (C-20), 18.7 (C-21), 33.9 (C-22), 26.1 (C-23), 45.8 (C-24), 29.1 (C-25), 19.8 (C-26), 19.0 (C-27), 23.0 (C-28), 12.2 (C-29), 21.5 (OAc), 21.5 (OAc), 170.2 (OAc), 170.7 (OAc).

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