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TERRACINOLIDES FROM *EUPHORBIA TERRACINA*

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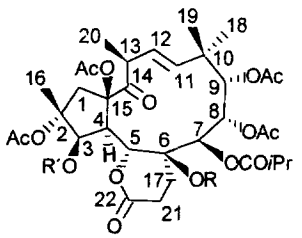
Key Word Index—*Euphorbia terracina*; Euphorbiaceae; bishomoditerpene lactones; bishomojatrophane; 17-ethyljatrophane; terracinolides.

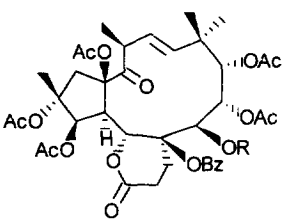
Abstract—The aerial parts of *Euphorbia terracina* yielded five new bishomoditerpene lactones, named terracinolides C–G, which display the novel C_{22} 17-ethyljatrophane framework.

INTRODUCTION

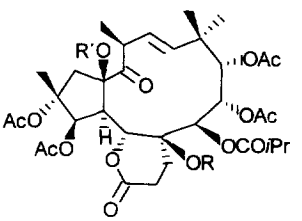
The large genus *Euphorbia* has been the object of numerous chemical studies [1]. As a part of our recently started research program on the chemistry of this genus, we have investigated *Euphorbia terracina* L., which grows mainly in sandy terrains, near the shore [2]. During previous work on this species, the occurrence of common triterpenes, flavonoids and coumarins was reported [3 and references therein]. Very recently, we have communicated the isolation from *E. terracina* of two new bishomoditerpene lactones, which were named terracinolides A **1** and B **2** [4]. These compounds show a novel C_{22} framework, formally derived from the jatrophane system by attachment of a two-carbon fragment to C-17. The structures of both products were deduced from NMR findings and X-ray analyses. In the present paper, we wish to report on the structures of five further C_{22} lactones with structures **3**–**7**, structurally close to **1** and **2**, which have been named in analogy terracinolides C–G, respectively.



1 R = Bz R′ = Ac
2 R = R′ = Ac
3 R = Ac R′ = H



4 R = Ac
5 R = COEt



6 R = COiPr R′ = Ac
7 R = Ac R′ = H

RESULTS AND DISCUSSION

The NMR data of lactone **3**, $C_{36}H_{50}O_{16}$ (Table 1), which we have named terracinolide C, were close to those of **2** [4]. Molecular formula and NMR data indicated the presence of an acetate group less than in the latter product. The other signals appeared more or less in the same positions in the spectra of both compounds, except that of H-3 which was shifted over 1 ppm at higher field in **3**. This and the differences in the chemical shifts of the ^{13}C NMR signals (Table 2) led us to conclude that the latter was the 3-deacetyl derivative of **2**. Acetylation of **3** to **2** gave support to this conclusion.

The structures of compounds **4**–**7** were closely related to those of **1**–**3**, judging from the similarity of their NMR data (Tables 1 and 2). These indicated that all four compounds were polyacylated derivatives of the same parent heptahydroxy lactone, and only differed in the structure of the ester residues. While the nature of the latter was deduced from their characteristic NMR signals, their location was established by a combination of NOE measurements and 2D heteronuclear COSY long-range correlations (HMBC) [4]. By means of this methodology, **4** was found to be a hexaacetate-benzoate of the parent lactone, with the

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Table 1. ^{1}H NMR data of terracinolides C–G (**3**–**7**)

H	**3**	**4***	**5***†	**6**	**7**
H-1α	2.92 *d*‡ (17)	3.24 *d*‡ (17)	3.10 *d*‡ (17)	3.09 *d* (17)	2.79 *d* (16)
H-1β	2.75 *d*‡ (17)	2.58 *d* (17)	2.58 *d* (17)	2.59 *d* (17)	2.10 *d* (16)
H-3	4.70 *br s*	5.80 *d* (3.8)	5.88 *d* (3.8)	5.82 *d* (3.5)	5.77 *d* (4)
H-4	3.60 *br d* (8.8)	3.93 *dd* (9.5; 3.8)	3.94 *dd* (9.5; 3.8)	3.80 *dd* (8.8; 3.5)	3.76 *dd* (8.8; 4)
H-5	5.66 *d* (8.8)	5.91 *d* (9.5)	5.90 *d* (9.5)	5.66 *d* (8.8)	5.38 *d* (8.8)
H-7	6.10 *s*	6.29 *s*	6.34 *s*	6.10 *s*	6.13 *s*
H-8	5.59 *s*	5.72 *s*	5.73 *s*	5.57 *s*	5.52 *s*
H-9	4.86 *s*	4.98 *s*	4.97 *s*	4.85 *s*	4.86 *s*
H-11	5.90 *d* (16)	5.98 *d* (16)	6.02 *d* (16)	5.92 *d* (16)	6.03 *d* (16)
H-12	5.48 *dd*‡ (16; 10)	5.54 *dd* (16; 10)	5.54 *dd* (16; 10)	5.46 *dd* (16; 10)	5.36 *dd* (16; 10)
H-13	4.01 *dq* (10; 6.5)	3.76 *dq* (10; 6.5)	3.88 *dq* (10; 6.5)	3.91 *dq* (10; 6.5)	4.00 *dq* (10; 6.5)
H-16	1.69 *s*	1.56 *s*	1.56 *s*	1.57 *s*	1.58 *s*
H-17α	2.44 *m*§	2.73 *ddd* (15; 15; 4.5)	2.72 *ddd* (15; 15; 4.5)	2.45 *m*§	2.40 *m*§
H-17β	1.90 *br m*	1.95 *br m*	1.90 *br dd* (15; 6.5)	1.70 *br m*	1.88 *br dd* (15; 6)
H-18	0.90 *s*‡	0.95 *s*	0.95 *s*	0.90 *s*	0.92 *s*
H-19	1.25 *s*‡	1.44 *s*	1.44 *s*	1.25 *s*	1.34 *s*
H-20	1.32 *d* (6.5)	1.19 *d* (6.5)	1.20 *d* (6.5)	1.30 *d* (6.5)	1.33 *d* (6.5)
H-21α	2.44 *m*§	2.53 *br dd* (15; 4.5)	2.52 *br dd* (15; 4.5)	2.45 *m*§	2.40 *m*§
H-21β	3.32 *ddd* (15; 15; 6)	3.40 *ddd* (15; 15; 6.5)	3.41 *ddd* (15; 15; 6.5)	3.27 *ddd* (15; 15; 6)	3.26 *ddd* (15; 15; 6)
OAc	2.25 *s*, 2.12 *s* 2.07 *s*, 2.03 *s* 2.00 *s*	2.26 *s*, 2.13 *s* 2.04 *s*, 2.03 *s* 2.01 *s*, 1.99 *s*	2.28 *s*, 2.04 *s* 2.01 *s*, 2.00 *s* 1.98 *s*	2.27 *s*, 2.07 *s* 2.01 *s*, 2.00 *s* 1.96 *s*	2.27 *s*, 2.04 *s* 2.01 *s* (×2) 2.00 *s*
OCOiPr	2.55 *sept* (7) 1.19 *d* (7) 1.15 *d* (7)			2.50 *m*§ 1.22 *d* (7), 1.20 *d* (7) 1.19 *d* (7), 1.17 *d* (7)	2.55 *sept* (7) 1.22 *d* (7) 1.20 *d* (7)

δ in ppm and *J* (parentheses) in Hz (400 MHz, $CDCl_3$, 25).
*OBz signals: 7.90 *dd* (2H; 8; 1.5), 7.60 *tt* (1H; 8; 1.5), 7.47 *t* (2H; 8).
†EtCO signals: 2.46 *dq* (18; 7.5), 2.29 *dq* (18; 7.5), 1.20 *t* (3H, 7.5).
‡Somewhat broadened.
§Overlapped signal.

benzoate group being bound to the tertiary 6-OH, as in **1**. Compound **5** was structurally similar to **4**, except that a propionate group replaced the 7-acetate fragment. In the same way, **6** was similar to **1** with the only replacement of the benzoate group of the latter by an isobutyrate moiety. As **3**, **7** differed from the other compounds in that it showed one free hydroxyl group. In contrast with **3**, however, this was not one of the secondary hydroxyls, as the signals of the geminal hydrogens remained practically in the same zone of the spectrum. Therefore **7** had a free tertiary OH group, which was located at C-15 on the basis of the characteristic shifts in the ^{13}C NMR signals of C-1, C-14 and C-15 (Table 2).

The structural type found in the lactones isolated from *E. terracina* does not exhibit any related counterpart in terpenes from other natural sources. As far as we may be allowed to speculate, the two-carbon fragment attached to C-17 in the jatrophane system could possibly arise through opening of a 5,17-epoxide by a nucleophillic C_2 unity (from acetate or malonate), followed by lactone ring closure (see Scheme 1). To the best of our knowledge, no such C—C bound diterpene-acetate adducts have been reported in the literature so far.

EXPERIMENTAL

NMR spectra at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$ (22). Optical rotations at 22 . MPCC: silica gel Merck (particle size 25–40 μm), gradient elution with the solvent mixts indicated in each case. Reverse-phase CC: silanized silica gel Merck (Art. 07719). HPLC: LiChrosorb RP-8 (250 × 8 mm), elution with MeOH–H_2O mixts.

Plant material. Aerial parts of *E. terracina* were collected in the shore near El Saler (province of Valencia, Spain), in June 1992. A voucher specimen (BCF-37210) has been deposited in the Herbarium of the Laboratory of Botany, Faculty of Pharmacy, University of Barcelona, Spain (Prof. J. Vallès Xirau).

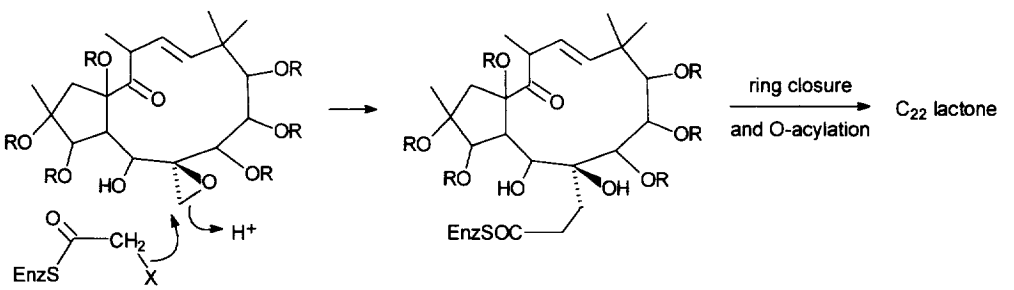
Extraction and chromatography. The plant material

Table 2. ^{13}C NMR data of terracinolides C–G (**3**–**7**)

C	3	4	5*	6	7
C-1	49.9	48.4	49.3	49.4	52.3
C-2	88.1	87.0	86.7	87.0	87.4
C-3	77.4	79.3	78.7	78.3	79.1
C-4	46.6	45.8	45.8	45.7	44.6
C-5	73.2	73.0	72.8	71.9	72.2
C-6	80.2	80.2	80.5	79.8	81.0
C-7	66.8	67.7[a]	67.7[a]	66.4	66.6
C-8	67.2	67.8[a]	67.8[a]	67.2	67.2
C-9	81.8	81.6	81.7	81.6	81.3
C-10	39.9	40.0	40.0	39.9	39.9
C-11	134.4	135.4	135.4	134.5	136.3
C-12	130.9	130.3	130.3	130.7	129.1
C-13	43.1	43.2	43.1	43.3	43.6
C-14	204.9	202.0	202.2	204.0	213.2
C-15	90.7	90.4	90.3	90.3	84.4
C-16	18.2	18.4	18.3	17.8	18.3
C-17	25.5	26.7	26.8	25.8	25.1
C-18	26.1	25.8	25.9	26.4	26.1
C-19	23.0	23.1	23.1	22.5	22.5
C-20	20.6	20.6	20.6	20.5	21.4
C-21	28.9	28.9	29.0	29.0	28.8
C-22	172.9	172.1	172.1	172.2	172.5
OAc	170.0, 169.9	169.7 (×2)	169.8, 169.7	169.9, 169.8	170.1, 169.8
	169.7, 169.5	169.4, 169.3	169.2, 169.0	169.0, 168.9	169.3 (×2)
	169.3, 22.6	168.8, 168.5	168.5, 22.3	168.5, 22.4	169.1, 22.4
	22.5, 21.2	22.3, 21.1	21.1, 21.0	21.3, 20.9	22.3, 21.0
	21.0, 20.6	21.0, 20.9	20.6, 20.4	20.7, 20.6	20.8, 20.7
		20.6, 20.5			
OCOiPr	174.2, 33.9			176.7, 174.5	174.6, 34.2
	18.5, 17.9			35.1, 34.1	18.8, 18.0
				19.6, 18.7	
				17.9, 17.8	
OBz		165.9, 133.7	166.0, 133.7		
		130.2, 129.7	130.3, 129.7		
		128.2	128.2		

δ in ppm (100 MHz, $CDCl_3$, 25). Signals have been assigned by means of 2D-NMR experiments.
*EtCO signals: 173.2, 27.4, 8.3.
[a]Signals with this superscript may be interchanged within the same column.

(680 g of aerial parts) was processed according to the procedure we have recently described [4]. The extract obtained after elution from the reverse-phase silica gel column with methanol–water 65:35 was pre-fractionated by CC on silica gel (A, hexane-Et_2O 1:1; B, Et_2O; C, Et_2O–MeOH 6:1). Column chromatography of fr. A allowed only the isolation of waxes, common triterpenes and other less interesting



Scheme 1. Possible biogenesis of lactones **1** and **2** by incorporation of a C_2 unit (from acetate or malonate) into a jatrophane precursor.

compounds. MPCC of fr. B (elution with hexane-EtOAc 10:1), followed where necessary by CC, prep. TLC or HPLC, allowed the isolation of lactones **1** (240 mg), **2** (178 mg), **3** (24 mg), **4** (21 mg), **5** (20 mg), **6** (30 mg) and **7** (22 mg).

Terracinolide C (**3**). Oil, $[\alpha]_D$ +25.5 ($CHCl_3$; *c* 0.55); IR ν_{max}^{film} cm^{-1}: 3480 (*br*, OH), 1766, 1758, 1750, 1746, 1740, 1730; EIMS (probe) *m/z* (rel. int.): 738.3123 $[M]^+$ (3), 710 $[M—CO]^+$ (7), 650 $[M—CO—HOAc]^+$ (43), 608 $[M—CO—HOAc—C_2H_2O]^+$ (18), 590 $[M—CO—2HOAc]^+$ (12), 548 $[M—CO—2HOAc—C_2H_2O]^+$ (5), 488 $[M—CO—3HOAc—C_2H_2O]^+$ (9), 460 $[M—CO—2HOAc—i$PrCOOH$—C_2H_2O]^+$ (12), 400 $[M—CO—3HOAc—i$PrCOOH$—C_2H_2O]^+$ (16), 340 $[M—CO—4HOAc—i$PrCOOH$—C_2H_2O]^+$ (34), 109 (70), 96 (66), 71 (100). Calc. for $C_{36}H_{50}O_{16}$, M_r = 738.3099; NMR, Tables 1 and 2.

Terracinolide D (**4**). Oil, $[\alpha]_D$ +37.5 ($CHCl_3$; *c* 0.8); IR ν_{max}^{film} cm^{-1}: 1767, 1755, 1748, 1728; EIMS (probe) *m/z* (rel. int.): 814.3083 $[M]^+$ (7), 786 $[M—CO]^+$ (40), 744 $[M—CO—C_2H_2O]^+$ (7), 684 $[M—CO—C_2H_2O—HOAc]^+$ (36), 624 $[M—CO—C_2H_2O—2HOAc]^+$ (8), 105 (100). Calc. for $C_{41}H_{50}O_{17}$, M_r = 814.3048; NMR, Tables 1 and 2.

Terracinolide E (**5**). Oil, $[\alpha]_D$ +50 ($CHCl_3$; *c* 0.8); IR ν_{max}^{film} cm^{-1}: 1766, 1751, 1724; EIMS (probe) *m/z* (rel. int.): 828.3240 $[M]^+$ (11), 800 $[M—CO]^+$ (42), 758 $[M—CO—C_2H_2O]^+$ (8), 698 $[M—CO—C_2H_2O—HOAc]^+$ (40), 638 $[M—CO—C_2H_2O—2HOAc]^+$ (6), 105 (100). Calc. for $C_{42}H_{52}O_{17}$, M_r = 828.3204; NMR, Tables 1 and 2.

Terracinolide F (**6**). Oil, $[\alpha]_D$ +17 ($CHCl_3$; *c* 0.6); IR ν_{max}^{film} cm^{-1}: 1767, 1755, 1744, 1730; EIMS (probe) *m/z* (rel. int.): 808.3517 $[M]^+$ (10), 780 $[M—CO]^+$ (30), 738 $[M—CO—C_2H_2O]^+$ (6), 678 $[M—CO—C_2H_2O—HOAc]^+$ (28), 618 $[M—CO—C_2H_2O—2HOAc]^+$ (8), 203 (48), 192 (73), 112 (34), 71 (100). Calc. for $C_{40}H_{56}O_{17}$, M_r = 808.3517; NMR, Tables 1 and 2.

Terracinolide G (**7**). Oil, $[\alpha]_D$ +14° ($CHCl_3$; *c* 4.5); IR ν_{max}^{film} cm^{-1}: 3450 (*br*, OH), 1763, 1752, 1744, 1730; EIMS (probe) *m/z* (rel. int.): 738.3096 $[M]^+$ (26), 710 $[M—CO]^+$ (6), 678 $[M—HOAc]^+$ (42), 650 $[M—CO—HOAc/M—i$PrCOOH$]^+$ (60), 636 $[M—HOAc—C_2H_2O]^+$ (10), 618 $[M—2HOAc]^+$ (14), 590 $[M—CO—2HOAc/M—i$PrCOOH$—HOAc]^+$ (6), 576 $[M—2HOAc—C_2H_2O]^+$ (12), 530 $[M—CO—3HOAc/M—i$PrCOOH$—2HOAc]^+$ (8), 516 $[M—3HOAc—C_2H_2O]^+$ (8), 470 $[M—CO—4HOAc/M—i$PrCOOH$—3HOAc]^+$ (10), 109 (67), 96 (64), 71 (100). Calc. for $C_{36}H_{50}O_{16}$, M_r = 738.3099; NMR, Tables 1 and 2.

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