Pergamon

PII: S0031-9422(97)00018-6

Phytochemistry, Vol. 45, No. 3, pp. 563–570, 1997

0031 9422/97 $17.00+0.00

INGENANE AND LATHYRANE DITERPENES FROM THE LATEX OF *EUPHORBIA CANARIENSIS*

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(*Received in revised form* 2 *December* 1996)

Key Word Index—*Euphorbia canariensis*; Euphorbiaceae; latex; diterpenes; ingenanes; ingenol esters; lathyranes; ingol epimers.

Abstract—The latex of *Euphorbia canariensis* yielded, in addition to five known ingenol esters, the ingenane derivatives ingenol 3-angelate 5,20-diacetate and 5-deoxyingenol 3-angelate 20-acetate, and the lathyrane derivatives 2,3-di*epi*ingol 7,12-diacetate 8-benzoate, 2,3-di*epi*ingol 7,12-diacetate 8-isobutyrate and 2-*epi*ingol 3,7,12-triacetate 8-benzoate. The structures were established with the aid of spectroscopic methods, mainly NMR, and molecular mechanics calculations. They were also supported by the results of some chemical transformations. ©1997 Elsevier Science Ltd. All rights reserved

INTRODUCTION

Within the family Euphorbiaceae, the sixth largest among flowering plants, the genus *Euphorbia* L. alone accounts for almost a sixth of the whole group [1, 2]. In recent treatments of its true circumscription [2], well over 1000 species are ascribed to this genus. Many of them have been the object of chemical and pharmacological investigations because of the irritant and carcinogenic properties of their lattices [3–6]. These biological properties have been traced back in many cases to the presence of certain types of diterpenes, most particularly phorbol derivatives, which have the tigliane framework [6, 7]. Further diterpenes belonging to other skeletal types, e.g. ingenane derivatives, are also characterized by similarly strong pharmacological effects [6].

The latex of *E. canariensis* was previously investigated [8 and refs therein]. Aside from other miscellaneous components, three ingenol derivatives were reported from the latex of specimens grown in the United States [8]. The proposed structures were erroneous, however, as to the locations of the ester residues. The correct structures **1**–**3** were published some time later [9]. As a part of our recent interest in the chemistry of the genus *Euphorbia* [10], we herein communicate our results on the latex obtained from *E. canariensis* collected in the Canary Islands.

RESULTS AND DISCUSSION

The latex of *E. canariensis* yielded seven ingenol esters (**1**–**7**) and three lathyrane derivatives (**9**–**11**) structurally related to ingol. From the former, compounds **1**–**3** correspond to those isolated in previous research [9], whereas **4** and **5** have been reported in other species of the genus [11, 12]. However, compounds **6**, **7**, **9**, **10** and **11** are, to the best of our knowledge, new natural products.

The signals in the ^{1}H NMR spectrum of **6** (Table 1) clearly indicate that the compound is an ingenol triester bearing an angelate and two acetate residues. This conclusion is supported by ^{13}C NMR data (Table 2). Chemical shift considerations further indicate that the ester moieties are located at the hydroxyl groups bound to C-3, C-5 and C-20. The precise locations of the individual acyl groups was deduced from the fact that **6** was obtained by acetylation of **1**. Compound **6** is therefore ingenol 3-angelate 5,20-diacetate. This compound was previously described as a derivative of a product found in *E. hermentiana* [9, 11].†

The NMR spectra of compound **7** are similar to those of **6**, with the exception that signals from only one acetate group, three oxygenated carbon atoms, and an additional methylene signal at δ 43.7 are present in the ^{13}C NMR spectrum of the former (Table 2). The counterpart of the latter carbon signal in the ^{1}H NMR spectrum (Table 1) is a pair of doublets (J = 18.5 Hz) at δ 2.52 and 2.36, obviously from an allylic methylene. This carbon shows long-range correlations (HMBC) with H-3 and H-20, as do its hydrogens with C-4, C-6 and C-7. We therefore concluded that **7** is a diester of 5-deoxyingenol, specifically the

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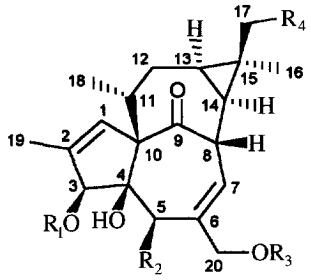
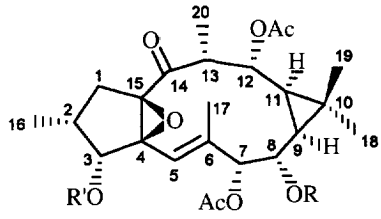
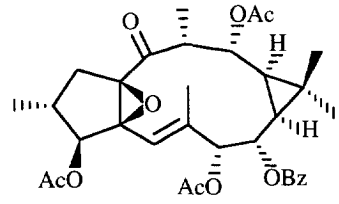
† The structure which appears in ref. [11] is erroneous (wrong configuration at C-15), but the correction was published later [9].



	R_1	R_2	R_3	R_4
1	Ang	OH	Ac	H
2	Ang	OH	H	OBz
3	Ang	OH	Ac	OBz
4	Ang	OH	Ac	OAc
5	Ang	OH	H	H
6	Ang	OAc	Ac	H
7	Ang	H	Ac	H
8	H	OH	Ang	OBz
8a	Ac	OAc	Ang	OBz



	R	R'
9	Bz	H
9a	Bz	Ac
9b	Ac	Ac
10	iBu	H



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3-angelate 20-acetate, as deduced from chemical shift considerations. Esters of 5-deoxyingenol have previously been described but are comparatively rare [6].

Compound **8** 17-hydroxyingenol 17-benzoate 20-angelate, was not present in the latex of *E. canariensis*, but was slowly found in some fractions containing ingenol diester (**2**), 17-hydroxyingenol 3-angelate 17-benzoate. This shows once more the ease with which intramolecular acyl migrations occur in ingenol esters, not only during partial hydrolyses [8, 11] but also during chromatographic manipulations. The ^{1}H NMR data of **8** and its acetate **8a** are described in the Experimental; their ^{13}C NMR data are given in Table 2.

High-resolution NMR data were not always provided in earlier reports of compounds **1–5**. We thus report the ^{1}H NMR data for all ingenane derivatives isolated in the present work, including the known ones, in Table 1, as well as the corresponding ^{13}C NMR data in Table 2. The configurations of all stereogenic centres have been reconfirmed with the aid of NOE measurements, whereas the carbon signals have been unequivocally assigned using HMQC/HMBC experiments. The latter further provided unequivocal evidence for the locations of the ester residues through observation of long-range H–C–O–COR correlations [13, 14].

The CIMS data of compound **9** (highest mass peak at *m/z* 555) indicate the molecular formula $C_{31}H_{38}O_9$. The NMR data (Tables 3 and 4) show the presence of a benzoate and two acetate groups. The hydrogen and carbon connectivities deduced from HMQC and HMBC experiments aided in establishing the lathyrane framework and allowed the conclusion that **9** is structurally close to a triester of ingol bearing two acetoxy groups at C-7 and C-12 and a benzoyloxy residue at C-8. In fact, acetylation of **9** gave **9a**, which has NMR data similar to those of ingol 3,7,12-triacetate 8-benzoate [15]. Several NMR features, however, that **9** is not an ingol derivative. A most notable point is the value of $J_{2,3}$ (5.5 Hz), which is quite different from that observed in true ingol esters (*ca* 8.5 Hz). Further relevant differences are observed in the chemical shifts of the H-1 protons, which appear in the spectra of ingol derivatives at *ca* 1.70–1.65 and 2.80–2.70 ppm [9, 15–20], a marked difference from those measured in **9** (Table 3). Finally, alkaline hydrolysis of **9** and subsequent acetylation yielded a tetraacetate **9b**, the spectral data of which are different from those of ingol tetraacetate [9]. Thus, compound **9** is a stereoisomer of ingol 7,12-diacetate 8-benzoate.

The similarity of chemical shift and coupling constant values in the fragment C-5 to C-13 of **9** with those published for ingol esters [9, 15–20] led us to conclude that configurational and conformational aspects of the 11-membered ring are essentially the same in all these compounds. The stereochemical differences were thus centred on the five-membered ring, most likely at C-2 and/or C-3. Unfortunately, the NOE data were not conclusive in the present case. For instance, a NOE was visible between the methyl group at C-2 (H-16) and *both* H-3 and 3-OH. Further NOEs were observed between H-2 and H-3, between H-3 and H-5, and between 3-OH and H-5. In view of this situation, we resorted to molecular modeling using 'MacroModel' [21]. Since the chemical shift values of the carbon atoms from C-6 to C-14 are essentially the same as in ingol esters [9, 18–20, 22], we maintained the β configuration for the epoxide ring (inversion to an α-epoxide would cause appreciable changes in these values, most particularly in the signals from carbons near to the five-membered ring). We then considered all four possible stereoisomers of ingol tetraacetate at C-2/C-3 (**A–D**, see Scheme 1) and used the aforementioned program to optimize their geometries. This was performed through a Batchmin

Table 1. ^{1}H NMR data of ingenane derivatives **1**–**7**

H	1	2*	3*	4	5	6	7
1	6.02 *br d* (1.5)	6.02 *br d* (1.5)	6.02 *br d* (1.5)	6.02 *br d* (1.5)	6.03 *br d* (1.5)	6.08 *br d* (1)	6.00 *br s*
3	5.55 *s*	5.57 *s*	5.57 *s*	5.55 *s*	5.52 *s*	5.04 *br s*	5.01 *s*
4-OH	3.45 *s*	3.60 *s*		3.45 *s*	3.50 *s*	3.30 *br s*	2.70 *br s*
5	3.89 *br d* (7)†	4.03 *br s*	3.86 *br s*	3.88 *br d* (5)‡	4.06 *br s*	5.42 *br s*	2.52 *d* (18.5)§
7	6.10 *br d* (4)	6.00 *br d* (4)	6.08 *br d* (4)	6.10 *br d* (4)	6.06 *br d* (4)	6.23 *br d* (4)	6.05 *br t* (2)
8	4.09 *br dd* (12; 4)	4.33 *br dd* (12; 4)	4.29 *br dd* (12; 4)	4.19 *br dd* (12; 4)	4.14 *br dd* (12; 4)	4.24 *br dd* (12; 4)	4.12 *br d* (11.5)
11	2.49 *m*	2.55 *m*	2.52 *m*	2.49 *m*	2.52 *m*	2.54 *m*	2.40 *m*
12α	1.76 *ddd* (16; 6.5; 5)	1.90 *m*¶	1.90 *m*¶	1.85 *ddd* (16; 6.5; 6.5)	1.75 *ddd* (15.5; 7; 6.5)	1.75 *ddd* (16; 6.5; 6)	1.79 *ddd* (15.5; 7; 6)
12β	2.22 *ddd* (16; 8.5; 2.7)	2.41 *ddd* (15.5; 9; 2.8)	2.39 *ddd* (15.5; 9; 2.8)	2.30 *ddd* (16; 8.5; 3)	2.25 *ddd* (15.5; 8.5; 3)	2.28 *m*¶	2.17 *ddd* (15.5; 8; 3)
13	0.69 *ddd* (8.5; 8.5; 6.5)	1.00 *m*¶	1.00 *m*¶	0.95 *m*¶	0.69 *ddd* (8.5; 8.5; 6.5)	0.70 *ddd* (9; 8.5; 6.5)	0.70 *ddd* (8; 8; 7)
14	0.95 *dd* (12; 8.5)	1.22 *m*¶	1.22 *dd* (12; 8.5)	1.15 *dd* (12; 8.5)	0.95 *dd* (12; 8.5)	0.96 *dd* (12; 8.5)	0.95 *m*¶
16	1.03 *s*	1.22 *s*	1.21 *s*	1.12 *s*	1.04 *s*	1.05 *s*	1.04 *s*
17	1.06 *s*	4.57 *d* (11.8)	4.52 *d* (11.8)	4.26 *d* (11.8)	1.08 *s*	1.07 *s*	1.10 *s*
		4.36 *d* (11.8)	4.36 *d* (11.8)	4.12 *d* (11.8)			
18	0.96 *d* (7)	0.98 *d* (7)	0.98 *d* (7)	0.97 *d* (7)	0.96 *d* (7)	0.98 *d* (7)	0.96 *d* (7)
19	1.78 *d* (1.5)	1.78 *d* (1.5)	1.78 *d* (1.5)	1.79 *d* (1.5)	1.79 *br s*	1.76 *d* (1)	1.78 *br s*
20	4.74 *br d* (12.5)	4.06 *br s*	4.66 *br d* (12.5)	4.74 *br d* (12.5)	4.14 *br s*	4.60 *br d* (12.5)	4.36 *br s*
	4.47 *br d* (12.5)	(2H)	4.38 *br d* (12.5)	4.47 *br d* (12.5)	(2H)	4.19 *br d* (12.5)	(2H)
OAc	2.04 *s* (3H)		1.98 *s* (3H)	2.05 *s* (6H)		2.24 *s*, 2.00 *s* (2 × 3H)	2.05 *s* (3H)
OAng	6.15 *qq* (7; 1.5)	6.14 *qq* (7; 1.5)	6.13 *qq* (7; 1.5)	6.17 *qq* (7; 1.5)	6.16 *qq* (7; 1.5)	6.10 *qq* (7; 1.5)	6.16 *qq* (7; 1.5)
	1.99 *dq* (7; 1.5)	2.00 *dq* (7; 1.5)	1.98 *dq* (7; 1.5)	2.00 *dq* (7; 1.5)	2.01 *dq* (7; 1.5)	1.96 *dq* (7; 1.5)	2.00 *dq* (7; 1.5)
	1.90 *dq* (1.5; 1.5)	1.90 *dq* (1.5; 1.5)	1.88 *dq* (1.5; 1.5)	1.91 *dq* (1.5; 1.5)	1.92 *dq* (1.5; 1.5)	1.89 *dq* (1.5; 1.5)	1.91 *dq* (1.5; 1.5)

δ in ppm and *J* (parentheses) in Hz (400 MHz, $CDCl_3$, 22°).
* OBz: 8.03 *dd* (2H; 8; 1.5), 7.56 *tt* (1H; 8; 1.5), 7.45 *t* (2H; 8).
† The 5-OH appears at δ 3.60 *d* (7).
‡ The 5-OH appears at δ 3.50 *br d* (5).
§ (5αH); 5βH appears at δ 2.36 *br d* (18.5).
¶ Overlapped signal.

Table 2. ^{13}C NMR data of ingenane derivatives **1–8a**

C	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**8a**
1	132.2	131.6	131.6	131.7	132.1	132.0	132.3	128.9	131.8
2	136.0*	136.2	136.2	136.4*	135.7	135.6	136.1	139.4	135.7
3	82.7	82.2	82.3	82.5	82.5	81.8	85.7	80.1	82.0
4	84.9	84.9	84.9	84.9	84.7	85.8	80.5	84.4	85.7
5	74.8	76.6	74.7	74.9	77.1	74.9	43.7	73.7	74.6
6	135.9*	139.7	136.4	136.3*	139.0	133.3	132.4	137.4	133.8
7	129.5	127.2	128.2	128.7	128.6	131.7	128.8	126.2	130.4
8	43.6	43.2	43.2	43.3	43.5	43.6	44.2	43.6	43.2
9	206.3	205.9	205.5	205.5	206.6	205.6	208.4	206.0	204.3
10	72.1	72.0	72.0	72.1	72.0	72.0	75.0	72.5	71.8
11	38.5	38.4	38.5	38.5	38.3	38.6	37.0	39.6	38.6
12	31.1	30.9	30.9	30.9	31.1	31.1	31.5	30.7	30.9
13	23.3	24.3	24.3	24.3	23.3	23.1	23.7	24.2	24.1
14	23.1	23.5	23.5	23.5	23.0	22.9	23.2	23.5	23.5
15	24.0	27.7	27.7	27.5	24.0	24.3	23.6	27.7	28.0
16	28.5	24.6	24.5	24.4	28.5	28.4	28.6	24.4	24.4
17	15.5†	66.2	66.1	65.6	15.5	15.4*	15.5*	66.2	66.2
18	17.3	16.9	16.9	17.0	17.3	17.0	18.2	16.9	16.6
19	15.6†	15.6	15.6	15.6	15.5	15.5*	15.6*	15.3	15.3
20	66.8	67.2	66.5	66.7	67.5	65.9	68.5	65.8	64.9
OAc	171.1		170.9	171.4, 171.0		170.8, 170.7	170.8		172.3, 170.6
	21.1		21.0	21.0 (×2)		20.9, 20.8	21.0		21.1, 20.7
OAng	168.4	168.4	168.2	168.3	168.5	169.1	168.6	167.9	167.2
	140.0, 127.1	139.8, 127.2	140.0, 127.0	140.2, 127.1,	140.0, 127.2	139.1, 127.4	139.9, 127.1	138.4, 127.6	138.4, 127.5
	20.8, 16.0	20.8, 15.9	20.7, 15.9	20.8, 16.0	20.8, 16.0	20.7, 15.8	20.7, 15.9	20.5, 15.7	20.5, 15.7
OBz		166.7	166.7					166.9	166.7
		133.0, 130.3	133.0, 130.2					133.0, 130.1	133.0, 130.2
		129.6, 128.4	129.5, 128.3					129.5, 128.4	129.5, 128.4

δ in ppm (100 MHz, $CDCl_3$, 22°). Signals have been assigned by means of 2D-NMR experiments.
*,† Signals with the same superscript may be interchangeable within the same column.

Table 3. ^{1}H NMR data of lathyrane derivatives **9**–**11**

H	**9***	**9a**	**9b**	**10**†,‡	**11**
1α	1.92 *m*§	2.01 *dd* (13.5; 7)	2.00 *dd* (13.5; 7)	1.95 *m*§	2.10 *m*§
1β	2.20 *m*¶	2.26 *dd* (13.5; 10.5)	2.25 *dd* (13.5; 10.5)	2.25 *m*¶	2.10 *m*§
2	1.92 *m*§	2.10 *m*§	2.10 *m*§	1.95 *m*§	1.90 *m*
3	3.98 *t* (5)	5.29 *d* (5.5)	5.28 *d* (5.5)	4.02 *t* (5)	5.05 *d* (8.8)
5	6.02 *br s*	5.68 *br s*	5.63 *br s*	6.00 *br s*	5.65 *br s*
7	5.24 *br s*	5.30 *br s*	5.19 *br s*	5.20 *br s*	5.08 *d* (1.5)
8	4.80 *dd* (10.5; 1.5)	4.82 *dd* (10.5; 1.5)	4.56 *dd* (10.5; 1.5)	4.60 *dd* (10.5; 1.5)	4.80 *dd* (11; 1.5)
9	1.40 *dd* (10.5; 9)	1.37 *dd* (10.5; 9)	1.20 *t* (10.5)	1.28 *dd* (10.5; 9)	1.46 *dd* (11; 9)
11	1.20 *dd* (11; 9)	1.24 *dd* (11; 9)	(2H)	1.14 *dd* (11; 9)	1.15 *dd* (11; 9)
12	4.90 *dd* (11; 4)	4.92 *dd* (11; 4)	4.86 *dd* (10.5; 4)	4.86 *dd* (11; 4)	4.90 *dd* (11; 4)
13	2.97 *dq* (4; 7)	2.99 *dq* (4; 7)	2.91 *dq* (4; 7)	2.95 *dq* (4; 7)	2.98 *dq* (4; 7)
16	0.98 *d* (6.5)	0.93 *d* (7)	0.92 *d* (7)	1.02 *d* (6.5)	1.03 *d* (7)
17	2.12 *br s*	2.14 *br s*	2.07 *br s*	2.09 *br s*	2.13 *br s*
18	1.11 *s*	1.16 *s*	1.11 *s*	1.09 *s*	1.15 *s*
19	0.80 *s*	0.83 *s*	0.84 *s*	0.84 *s*	0.82 *s*
20	1.03 *d* (7)	1.07 *d* (7)	1.05 *d* (7)	1.04 *d* (7)	1.05 *d* (7)
OAc	2.05 *s* (3H)	2.11 *s* (3H)	2.10 *s* (3H)	2.12 *s* (3H)	2.13 *s* (3H)
	2.04 *s* (3H)	2.09 *s* (3H)	2.09 *s* (3H)	2.09 *s* (3H)	2.08 *s* (3H)
		2.05 *s* (3H)	2.08 *s* (3H)		2.04 *s* (3H)
			2.00 *s* (3H)		
OBz	7.96 *dd* (2H; 8; 1.5)	7.98 *dd* (2H; 8; 1.5)			8.00 *dd* (2H; 1.5)
	7.52 *tt* (1H; 8; 1.5)	7.56 *tt* (1H; 8; 1.5)			7.57 *tt* (1H; 8; 1.5)
	7.40 *t* (2H; 8)	7.43 *t* (2H; 8)			7.44 *t* (2H; 8)

δ in ppm and J (parentheses) in Hz (400 MHz, $CDCl_3$, 22°).

* 3-OH: 2.50 *br d* (5).

† 3-OH: 1.65 *d* (5).

‡ OiBu: 2.48 *qq* (7; 7), 1.13 *d* (3H; 7), 1.11 *d* (3H; 7).

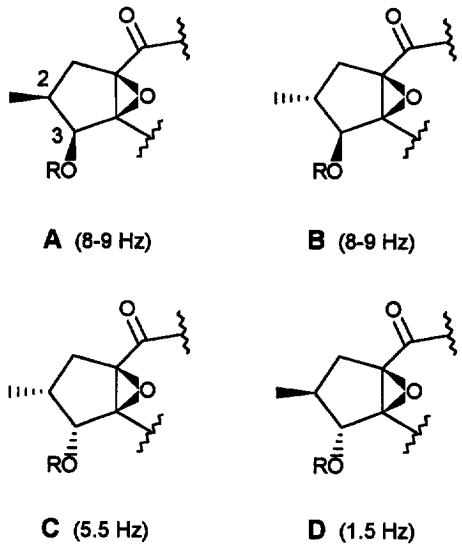
§ Overlapped signal.

¶ Non-first-order signal.

Table 4. ^{13}C NMR data of lathyrane derivatives **9–11**

C	9	9a	9b	10*	11
1	32.1	32.7	32.7	32.1	31.1
2	33.0	32.5	32.5	32.9	31.0
3	76.4	77.2	77.1	76.6	80.4
4	72.5	70.7	70.7	72.4	69.8
5	116.8	115.2	115.4	116.6	117.0
6	137.4	139.1	138.8	137.6	139.7
7	77.3	76.8	76.5	76.7	77.3
8	72.1	72.0	71.4	71.4	71.6
9	24.7	24.8	24.5	24.6	25.2
10	19.3	19.4	19.2	19.2	19.6
11	30.7	30.8	30.5	30.6	30.8
12	70.7	70.5	70.5	70.7	70.7
13	43.2	43.4	43.3	43.1	42.9
14	207.8	207.4	207.3	207.6	207.3
15	73.1	73.0	73.1	73.1	71.4
16	12.0	12.3	12.3	12.0	16.1
17	17.5	17.6	17.6	17.6	17.3
18	29.1	29.1	29.0	29.1	29.2
19	16.1	16.2	16.1	16.3	16.1
20	13.3	13.2	13.2	13.3	13.5
OAc	170.5, 169.9	170.3, 169.5, 169.0	170.4, 170.3, 169.6, 169.2	170.4, 169.8	170.8; 170.3, 169.9
	21.0, 20.9	21.0, 20.8, 20.6	21.0, 20.9 (×2), 20.6	21.1, 21.0	21.0 (×2), 20.7
OBz	165.8	165.8			165.7
	133.2, 129.7	133.2, 129.7			133.2, 129.7
	129.5, 128.4	129.5, 128.4			129.6, 128.5

δ in ppm (100 MHz, $CDCl_3$, 22°). Signals have been assigned by means of 2D-NMR experiments.
*OiBu: 176.3, 33.9, 18.8, 18.7.



Scheme 1. Calculated $J_{2,3}$ values (in parentheses) for ingol stereoisomers **A–D**.

conformational search and energy minimization [21], which provided the lowest energy conformers for each possible diasteroisomer. For two of them, the ingol-type derivative **A** and its 2-*epi*isomer **B**, $J_{2,3}$ values in the range 8–9 Hz were calculated. For the 2,3-di*epi*isomer **C**, the predicted $J_{2,3}$ was 5.5 Hz, while for the 3-*epi*isomer **D**, a $J_{2,3}$ value of *ca* 1.5 Hz was found. Thus, we concluded that a 2,3-di*epi*ingol derivative is present in the case of **9**, and that is therefore 2,3-di*epi*ingol 7,12-diacetate 8-benzoate. The interatomic distances and the NOEs predicted for this structure were in good agreement with the actual observations.

According to NMR evidence, compound **10** is very close to **9**. Chemical shifts and coupling constants are almost identical in both compounds (Tables 3 and 4), the only difference being the presence of an isobutyrate group in **10** instead of the benzoyl group found in **9**. Compound **10** is, therefore, 2,3-di*epi*ingol 7.12-diacetate 8-isobutyrate.

Compound **11** is closely related to **9a**, as evidenced from NMR data. All spectral data, including heteronuclear 2D NMR measurements, point to an ingol-type tetraester bearing acetoxy groups at C-3, C-7 and C-12, and a benzoyloxy group at C-8. One main difference with **9a** is the coupling constant $J_{2,3} = 8.8$ Hz. However, **11** is not an ingol ester, in view of the chemical shifts of the H-1 protons (Table 3) and of the five-membered ring carbons (Table 4) [9, 18–20, 22]. On the basis of the aforementioned molecular mechanics calculations [21] and of the value of $J_{2,3}$, we concluded that **11** is a stereoisomer of ingol displaying the **B**-type configuration in the five-membered ring. Compound **11** is thus 2-*epi*ingol 3,7,12-triacetate 8-benzoate.

This product represents the second report in the literature of a 2-*epi*ingol derivative. The first members of this compound class have been described very

recently and display NMR data close to those of **11** [23]. Aside from this, no epimers of ingol were previously reported in the literature. A careful examination of the published data yielded findings worth mentioning. For instance, the following $J_{2,3}$ values were previously published for various assumed ingol derivatives: 8.5 ± 0.5 Hz [9, 15–20], 5.5 Hz [14] and 1.3 Hz [13, 24]. Since, in principle, all of these compounds differ only in the nature of the ester residues, the aforementioned coupling constant should remain practically constant through the series within a range of 8.5 ± 0.5 Hz. With the aforementioned exception [23], all previously published compounds where $J_{2,3}$ is *ca* 8.5 Hz are in all probability ingol derivatives, since the chemical shift values of H-1α and H-1β are also quite similar to each other. However, this is not likely for the compounds where $J_{2,3}$ is 5.5 or 1.3 Hz. A structural revision might be advisable in these particular examples.

EXPERIMENTAL

NMR: $CDCl_3$ with an inverse probehead at 400 MHz (^1H) and 100 MHz (^{13}C), solvent signals as reference; CIMS, CH_4: Hewlett–Packard 5988A mass spectrometer; optical rotations: $CHCl_3$ at 22°; normal pressure CC: silica gel Südchemie AG (particle size 50–200 μm); reverse-phase silica gel silanized silica gel Merck (Art. 07719); HPLC: LiChrosorb RP-8 (250 × 8 mm), elution with MeOH–H_2O mixts, flow rate, 3 ml/min.

Plant material. The latex of *E. canariensis* (*ca* 90 g) was collected in Malpais de Güimar, Teneriffa, Canary Islands, in May 1993.

Extraction and chromatography. Dissolution of the latex in hot MeOH (1 l) and re-cooling to room temp gave rise to voluminous, white precipitate of common triterpenes [8], which was eliminated by filtration. Evaporation of the solvent *in vacuo* gave a whitish, oily material (*ca* 16 g). After dissolving this oil in the minimum amount of MeOH, reverse-phase silica gel was added (3 g of silica gel/g of extract) [10]. The solvent was then totally eliminated *in vacuo*. The powdery material obtained was placed on the top of a chromatographic column filled with the same type of silica gel and eluted under a slight Ar pressure (1.5–2 atm) firstly with water, then with MeOH–H_2O (7:3) and finally with MeOH. The water and MeOH frs were discarded as they only contained polar, ill-defined compounds and common triterpenes (mainly euphol and euphorbol), respectively. The middle fraction (*ca* 11 g) was subjected to further chromatographic separations as described below.

The middle fr. was subjected to CC on silica gel (elution with hexane–Et_2O 10:1 → Et_2O). The intermediate frs were further purified, where necessary, by prep. TLC and/or HPLC. This allowed the isolation of additional amounts of triterpenes and of the compounds mentioned in the text. The latter were eluted from the silica gel column in the following order of increasing polarity: **6** (8 mg), **7** (14 mg), **11** (17 mg), **1** (170 mg), **3** (176 mg), **10** (15 mg), **9** (220 mg), **2** (75 mg), **4** (7 mg) and **5** (3 mg). Compound **8** was not initially present in the extracts, but was slowly formed in some frs containing **2** after chromatographic manipulations.

Ingenol-3-angelate-5,20-diacetate (**6**). Oil, $[\alpha]_D$ +19° ($CHCl_3$; *c* 3); IR ν_{max}^{film} cm^{-1}: 3420 (*br*, OH), 1740, 1736, 1709, 1695 (ester and ketone C=O), 1655, 1462, 1373, 1242, 1169, 1034, 906, 892; CIMS (CH_4) *m/z* (rel. int.): 515.2660 $[M+H]^+$ (6), 455 $[M+H-AcOH]^+$ (5), 415 $[M+H-AngOH]^+$ (4), 355 $[M+H-AcOH-AngOH]^+$ (100), 295 $[M+H-2AcOH-AngOH]^+$ (90), 267 $[M+H-2AcOH-AngOH-CO]^+$ (20), 101 (50), 61 (58). Calcd for $C_{29}H_{39}O_8$, M = 515.2645; NMR, Tables 1 and 2. Identical by NMR and TLC with the product obtained by acetylation (Ac_2O/pyridine, room temp) of **1**.

5-Deoxyingenol 3-angelate 20-acetate (**7**). Oil, $[\alpha]_D$ +1.5° ($CHCl_3$; *c* 0.5); IR ν_{max}^{film} cm^{-1}: 3450 (*br*, OH), 1736, 1717, 1698, 1694 (ester and ketone C=O), 1453, 1376, 1235, 1155, 1034, 936, 883; CIMS (CH_4) *m/z* (rel. int.): 457.2602 $[M+H]^+$ (6), 439 $[M+H-H_2O]^+$ (2), 397 $[M+H-AcOH]^+$ (4), 379 $[M+H-H_2O-AcOH]^+$ (4), 357 $[M+H-AngOH]^+$ (15), 339 $[M+H-H_2O-AngOH]^+$ (4), 297 $[M+H-AcOH-AngOH]^+$ (100), 279 $[M+H-H_2O-AcOH-AngOH]^+$ (44), 269 $[M+H-H_2O-AcOH-AngOH-CO]^+$ (34), 101 (25), 61 (39). Calcd for $C_{27}H_{37}O_6$, M = 457.2590; NMR, Tables 1 and 2.

17-Hydroxyingenol 17-benzoate 20-angelate (**8**). Oil, $[\alpha]_D$ −7.5° ($CHCl_3$; *c* 2.9); IR ν_{max}^{film} cm^{-1}: 3430 (*br*, OH), 1715, 1700, 1452, 1377, 1268, 1146, 965, 715; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02 (2H, *dd*, J = 7.5, 1.5 Hz, *ortho*-aromatic), 7.54 (1H, *tt*, J = 7.5, 1.5 Hz, *para*-aromatic), 7.43 (2H, *t*, J = 8 Hz, *meta*-aromatic), 6.03 (1H, *br d*, J = 4.5 Hz, H-7), 6.02 (1H, *qq*, J = 7, 1.5 Hz, angelate olefinic), 5.88 (1H, *br d*, J = 1.5 Hz, H-1), 4.68 (1H, *d*, J = 13 Hz, H-20_a), 4.56 (1H, *br d*, J = 13 Hz, H-20_b), 4.55 (1H, *d*, J = 11.8 Hz, H-17_a), 4.45 (1H, *d*, J = 11.8 Hz, H-17_b), 4.40 (1H, *br s*, 4-OH), 4.32 (1H, *br s*, H-3), 4.30 (1H, *br dd*, J = 12, 4.5 Hz, H-8), 3.90 (1H, *br s*, 3-OH), 3.66 (1H, *br d*, J = 10 Hz, H-5), 3.45 (1H, *br d*, J = 10 Hz, 5-OH), 2.40 (2H, *br m*, H-11, H-12β), 1.89 (3H, *dq*, J = 7, 1.5 Hz, angelate Me), 1.82 (1H, overlapped *m*, H-12α), 1.80 (6H, *br s*, H-19, angelate Me), 1.22 (3H, *s*, H-16), 1.22 (1H, overlapped *m*, H-14), 0.95 (1H, overlapped *m*, H-13), 0.95 (3H, *d*, J = 7 Hz, H-18); ^{13}C NMR, Table 2. Acetylation (Ac_2O/pyridine, room temp) gave **8a**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02 (2H, *dd*, J = 7.5, 1.5 Hz, *ortho*-aromatic), 7.54 (1H, *tt*, J = 7.5, 1.5 Hz, *para*-aromatic), 7.43 (2H, *t*, J = 8 Hz, *meta*-aromatic), 6.24 (1H, *br d*, J = 4.5 Hz, H-7), 6.06 (1H, *br d*, J = 1.5 Hz, H-1), 6.02 (1H, *qq*, J = 7, 1.5 Hz, angelate olefinic), 5.40 (1H, *br s*, H-5), 4.95 (1H, *br s*, H-3), 4.48 (3H, *br m*, H-8, H-17_a, H-20_a), 4.38 (1H, *d*, J = 11.8 Hz, H-17_b), 4.25 (1H, *br d*, J = 12.5 Hz, H-20_b), 3.25 (1H, *br s*, 4-OH), 2.54 (1H, *m*, H-11), 2.40 (1H, *ddd*, J = 16, 9, 2.7 Hz, H-12β), 2.20 (3H, *s*, 5-OAc), 2.10

(3H, *s*, 3-OAc), 1.89 (3H, *dq*, $J = 7$, 1.5 Hz, angelate Me), 1.85 (1H, overlapped *m*, H-12α), 1.81 (3H, *dq*, $J = 1.5$, 1.5 Hz, angelate Me), 1.74 (3H, *br s*, H-19), 1.23 (3H, *s*, H-16), 1.22 (1H, overlapped *m*, H-14), 1.00 (1H, overlapped *m*, H-13), 1.00 (3H, *d*, $J = 7$ Hz, H-18); ^{13}C NMR, Table 2.

2,3-*Diepiingol* 7,12-*diacetate* 8-*benzoate* (**9**). Oil, $[\alpha]_D$ −25° ($CHCl_3$; *c* 3.4); IR ν_{max}^{film} cm^{-1}: 3500 (br, OH), 1736, 1721, 1705, 1698 (ester and ketone C=O), 1449, 1372, 1277, 1242, 1103, 992, 713; CIMS (CH_4) *m/z* (rel. int.): 555.2582 $[M+H]^+$ (3), 495 $[M+H-AcOH]^+$ (59), 433 $[M+H-PhCOOH]^+$ (100), 373 [M+H–PhCOOH–AcOH] (5), 313 [M+H–PhCOOH–2AcOH] (10), 123 (16), 61 (27). Calcd for $C_{31}H_{39}O_9$, $M = 555.2594$; NMR, Tables 3 and 4. Acetylation (Ac_2O/pyridine, room temp) gave **9a**, oil; $[\alpha]_D$ −34° ($CHCl_3$; *c* 3); IR ν_{max}^{film} cm^{-1}: 1744, 1732, 1713 (ester and ketone C=O); NMR, Tables 3 and 4. Alkaline hydrolysis of **9** (K_2CO_3, MeOH, room temp), followed by acetylation yielded **9b**, oil; $[\alpha]_D$ +10° ($CHCl_3$; *c* 0.4); IR ν_{max}^{film} cm^{-1}: 1747, 1739, 1732, 1709 (ester and ketone C=O); NMR, Tables 3 and 4.

2,3-*Diepiingol* 7,12-*diacetate* 8-*isobutyrate* (**10**). Oil; $[\alpha]_D$ −8.5° ($CHCl_3$, *c* 1.4); IR ν_{max}^{film} cm^{-1}: 3500 (*br*, OH), 1744, 1728, 1713, 1698 (ester and ketone C=O), 1470, 1438, 1370, 1242, 1154, 958, 945, 868, 729; CIMS (CH_4) *m/z* (rel. int.): 521.2772 $[M+H]^+$ (3), 461 $[M+H-AcOH]^+$ (66), 433 $[M+H-iBuOH]^+$ (100), 373 $[M+H-iBuOH-AcOH]^+$ (10), 313 [M+H–iBuOH–2AcOH] (22), 295 (21), 267 (9), 123 (6), 61 (27). Calc. for $C_{28}H_{41}O_9$, M = 521.2750; NMR, Tables 3 and 4.

2-*Epiingol* 3,7,12-*triacetate* 8-*benzoate* (**11**). Oil: $[\alpha]_D$ −41° ($CHCl_3$; *c* 1); IR ν_{max}^{film} cm^{-1}: 1745, 1737, 1730, 1712 (ester and ketone C=O), 1452, 1369, 1273, 1234; CIMS (CH_4) *m/z* (rel. int.): 597.2680 $[M+H]^+$ (8), 537 $[M+H-AcOH]^+$ (85), 475 $[M+H-PhCOOH]^+$ (100), 105 $[PhCO]^+$ (72). Calcd for $C_{33}H_{41}O_{10}$, $M_r = 597.2699$; NMR, Tables 3 and 4.

The known compounds were identified by comparison of their NMR spectra with literature data.

Acknowledgements—We thank the I.V.E.I. for financial support of this research (project CPE-053). Thanks are also due to Dr J. Jakupovic, Technical University of Berlin, Germany, for helpful discussions and for the exchange of information prior to publication; to Prof. A. D. Kinghorn, University of Illinois at Chicago, U.S.A., for providing us with spectral data of ingol tetraacetate; and to Ms Laura J. Gatzkiewicz for revision of the English manuscript.

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