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SESQUITERPENE LACTONES FROM *ARTEMISIA LUCENTICA*

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Key Word Index—*Artemisia lucentica*; Compositae; Anthemideae; monoterpenes; sesquiterpene lactones; germacranolides; eudesmanolides; guaianolides; nor-elemanolide; bisabolenes.

Abstract—The aerial parts of *Artemisia lucentica* yielded, in addition to several known compounds, a bicyclic monoterpene ketone, two germacranolides, an eudesmanolide, a 10-*epi*eudesmanolide, a 2-norelemanolide and three bisabolene derivatives. The stereochemistry of a germacranolide, described as 2α-hydroxyartemorin in a previous investigation of the species, has now been corrected and the compound has been renamed lucentolide. © 1997 Elsevier Science Ltd. All rights reserved

INTRODUCTION

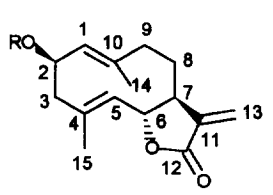
The large genus *Artemisia* has been the object of numerous chemical studies [1]. The Spanish species *A. lucentica* O. Bolòs, Vallès et Vigo (previously named *A. hispanica* Lam. non Weber ex Stechm.) has already been investigated by our group. We reported the occurrence of various phenolics [2] and sesquiterpenoids [3], among the latter the new germacranolide 2α-hydroxyartemorin. We have now reinvestigated the same species with the aim of looking for the presence of further minor metabolites, particularly terpenes, which could have been overlooked at that time.

RESULTS AND DISCUSSION

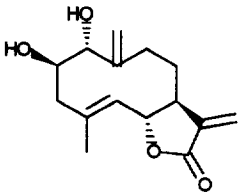
As a result of our reinvestigation of this plant, we have found again all of the compounds isolated during our previous work, except for tamaulipin A, as well as eight new ones with structures **1b**, **2**, **5**, **6** and **9**–**13**. Further known compounds isolated from the species, but not detected in our first investigation, were the sesquiterpene lactones **3** [4, 5], **4** [6], deacetoxymatricarin [7], 1β-hydroxyarbusculin A [7], artecanin [8] and *iso-seco*tanapartholide [9], as well as the monoterpene ketone **14** [10]. Methyl ester **7** was also found, but its origin might be called into question.

Compound **1b**, isolated in a very small amount, showed IR bands for lactone and ester groups (1760, 1735 cm^{-1}). The NMR signals (Tables 1 and 3) were very broad at room temperature suggesting a marked conformational flexibility. At 58° the spectral lines became sharp enough to permit their interpretation. Its spectral properties turned out to be identical with those of the acetate of a compound isolated by us in our first investigation of *A. lucentica* (= *A. hispanica*) [3], which we had identified as tamaulipin A (2α-hydroxycostunolide) on the basis of its easy rearrangement to a known elemane aldehyde [11]. However, a comparison with the reported data of 2α-acetoxycostunolide (tamaulipin A acetate) [11] established that both compounds were different. Consequently, **1b** is the corresponding epimer at C-2, 2β-acetoxycostunolide, a conclusion further supported by NOE measurements and molecular mechanics calculations (see discussion below). Our previous structural assignment was thus erroneous and we actually isolated **1a** (2β-hydroxycostunolide), which was not detected, however, in the present work.

The physical and chromatographic properties, as well as the ^1H NMR data of lactone **2** (Table 2) were identical with those of the germacranolide we previously described as 2α-hydroxyartemorin [3]. The molecule of **2** is also conformationally flexible, as evidenced by the broadened signals in the NMR spectra (Tables 2 and 3). In view of the erreneous stereochemical assignment of **1a**/**1b**, we reinvestigated the stereochemistry of **2** by NOE measurements and found that some of them could not be explained on the basis of the current structure. For instance, a distinct NOE detected between H-2 and H-5 required, as in the previous case, an inversion of the initially proposed configuration at C-2. Other significant NOEs were observed between one of the H-14 hydrogens and both H-1 and H-2; of the same H-14 with H-8β and H-15; and of H-15 with H-1, H-2, H-6, H-7 and H-14. The explanation of these NOEs required the consideration of two or more main conformations. We then had recourse to a combination of variable temperature NMR measurements and molecular mechanics calculations [12, 13].



1a R=H
1b R=Ac



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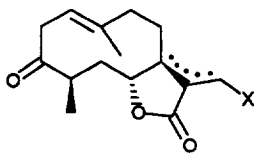
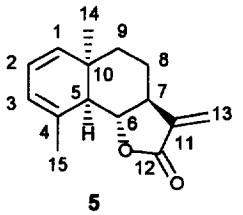


3 X=H $\Delta^{11,13}$
4 X=OH $\Delta^{7,11}$



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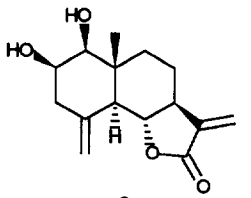

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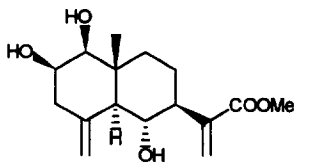

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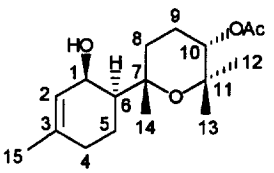

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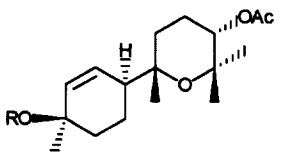
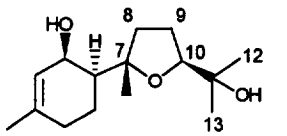


9 R=OH
10 R=H



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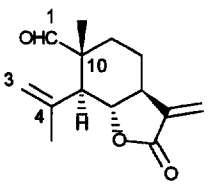

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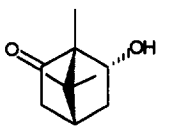

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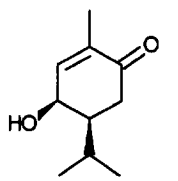

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Because of the poor solubility of **2** in $CDCl_3$, especially at low temperature, CD_3OD was now used for the NMR measurements. Increasing the temperature led, initially, to further signal broadening, followed by re-sharpening at temperatures above 333 K, slightly below the boiling point of the solvent. This indicates that several conformers are already present to an appreciable extent at room temperature. A similar phenomenon was observed by lowering the temperature. Some signals became first broader and then again sharper, specially below 243 K. At temperatures below 273 K, signals from a second conformer began to be visible, followed by signals of a third one below 243 K. In the range from 243 to 223 K, the ^1H NMR spectrum did not change appreciably.

These conformers, named A, B and C, respectively, with approximate relative populations of, respectively 65, 15 and 20%, displayed clear differences in some of their chemical shift values and also in some key coupling constants (Table 2). For instance, conformers A and C display H-6 signals in the form of triplets with $J_{5,6} = J_{6,7} = 10$ Hz. This strongly suggests conformations where H-5, H-6 and H-7 show the most usual *anti/anti* arrangement, with C-4-Me (H-15) pointing upwards. In contrast, conformer B shows $J_{5,6} = 7$ Hz and $J_{6,7} = 10.5$ Hz, which suggests a conformation where H-5 and H-6 are in an approximate *syn* relationship, with H-15 pointing downwards. In view of these conclusions, we performed molecular mechanics calculations [12, 13] for the stereoisomers with either the 1β,2β-dihydroxy or the 1α,2β-dihydroxy germacranolide structure. Only the main conclusions drawn from these calculations are presented here. They have led us to propose structure **2** as the correct structure and stereochemistry of the germacranolide under study. Scheme 1 shows the three main conformations with the lowest energy values found by either of the aforementioned programmes and their tentative assignment of conformers A, B and C, as deduced from the NMR findings. Similar conformations, although with different relative energies, were found for the 1β,2β-dihydroxy isomer but a small value of $J_{1,2}$ (less than 3 Hz) was predicted for all of them. This clearly disagrees with the experimental value $J_{1,2} = 9$ Hz, which is easily explained with the essentially *anti* coplanar arrangement of H-1 and H-2 in each of the three conformations A, B and C. Conformations A and C belong to the DU and UU

Table 1. ^{1}H NMR data of lactones **1b**, **5**, **6** and **12**

H	**1b***	**5**	**6**	**12**
1	4.92 *br m*†	5.28 *br d* (9.6)	3.42 *br d* (3)	9.50 *s*
2	5.78 *br t* (6)	5.82 *dd* (9.6; 5.2)	4.10 *m*†	—
3α			2.44 *br dddd*	5.04 *t* (1.5)
	2.50 *br m*†	5.70 *br dq* (5.2; 1.5)	(14; 2.5; 2; 2)	
3β			2.50 *dd* (14; 2.5)	4.80 *s*
5	4.90 *br d*† (10)	1.92 *br dd* (11; 1.5)	2.21 *br d* (11)	2.87 *br d* (11)
6	4.60 *t* (10)	3.90 *t* (11)	4.09 *t* (11)	4.08 *t* (11)
7	2.50 *br m*†	2.34 *ddddd*	2.53 *ddddd*	2.59 *ddddd*
		(11; 11; 4; 3.3; 3)	(13; 11; 3.5; 3.3; 3)	(13; 11; 3.3; 3; 3)
8α	2.10 *br m*†	2.02 *dddd*	2.04 *dddd*	2.18 *dddd*
		(12; 2; 2; 2)	(13; 3.5; 3; 3)	(13; 4; 3; 3)
8β	1.70 *br m*†	1.45 *m*†	1.62 *dddd*	1.62 *dddd*
			(13; 13; 13; 3.5)	(13; 13; 13; 3)
9α		1.76 *m*	1.35 *ddd*	1.82 *ddd*
	2.50 *br m*†		(14; 13; 3)	(13; 13; 4)
9β		1.45 *m*†	2.11 *ddd*	1.50 *ddd*
			(14; 3.5; 3)	(13; 3; 3)
13	6.24 *d* (3.5)	6.05 *d* (3.3)	6.08 *d* (3.3)	6.13 *d* (3.3)
	5.48 *d* (3.3)	5.38 *d* (3)	5.42 *d* (3)	5.46 *d* (3)
14	1.67 *br s*	1.00 *s*	0.94 *s*	1.15 *s*
15	1.82 *br s*	1.94 *br d* (1.5)	5.12 *br s*	1.75 *s*
			5.02 *br s*	

δ in ppm and *J* (parentheses) in Hz (400 MHz, $CDCl_3$, 25°).
* At 58°.
† Overlapped signal.

Table 2. Variable temperature ^{1}H NMR data of lactone **2**

H	**2***	**2**†	**2** (conf. A)‡	**2** (conf. B)‡	**2** (conf. C)‡
1	3.60 *br d* (9)	3.65 *br d* (9)	3.75 *d* (9)	3.45 *d* (9)	3.45 *m*§
2	3.92 *br ddd*	3.98 *br ddd*	3.96 *ddd*	3.93 *ddd*	4.15 *br m*
	(9; 9; 5)	(9; 9; 6)	(11; 9; 5)	(11; 9; 5)	
3α	1.84 *br m*	1.87 *br dd* (14; 9)		1.70 *br m*§	
3β	2.85 *br dd* (14; 5)	2.80 *br dd* (14; 6)		2.80–2.70 *br m*§	
5	5.20 *br d* (10)	5.30 *br d* (10)	5.43 *br d* (10)	5.60 *br d*§ (7)	5.10 *br d* (10)
6	4.37 *br t* (10)	4.50 *br t* (10)	4.51 *t* (10)	4.26 *dd* (10.5; 7)	4.72 *t* (10)
7	2.60 *br m*	2.71 *br dddd*	2.80–2.70 *br m*§	3.45 *m*§	2.80–2.70 *br m*§
		(10; 10; 3.5; 3)			
8α	2.20 *br m*	2.25 *br dd* (14; 9)		2.30–2.20 *br m*	
8β	1.56 *br ddd*	1.65 *br ddd*		1.60–1.50 *br m*	
	(13; 11; 11)	(14; 10; 10)			
9α	2.05 *br m*	2.10 *br dd* (16; 10)		2.03 *br dd* (17; 10)	
9β	2.40 *br m*	2.48 *br dd* (16; 9)		2.55–2.40 *br m*	
13	6.13 *d* (3.3)	6.08 *d* (3.5)	6.08 *d* (3.3)	6.12 *d* (3.3)	6.08 *d*§
	5.44 *br d* (3)	5.56 *d* (3)	5.60 *d* (3)	5.65 *d* (3)	5.60 *d*§
14	5.10 *br s*	5.10 *br s*		5.10 *br s*	
	4.84 *br s*	4.62 *br s*		4.80 *br s*	
15	1.72 *br s*	1.77 *br s*	1.70 *br s*	1.93 *br s*	1.72 *br s*

δ in ppm and *J* (parentheses) in Hz (400 MHz, CD_3OD).
* At 333 K.
† At 294 K.
‡ At 223 K.
§ Overlapped signal.

Table 3. ^{13}C NMR data of lactones **1b**, **2**, **5**, **6** and **12**

C	1b*	2†	5	6	12
1	128.5‡	79.4‡	133.3	78.4	203.2
2	73.3‡	73.2§	124.0	71.2	—
3	45.0	40.8§	118.1	41.5	116.6
4	140.0	142.0‡	136.3	138.6	139.8
5	125.1§	124.2§	51.1	53.2	51.2
6	81.7	80.8	83.2	79.0	80.1
7	≈50§	≈49¶	47.3	49.6	48.8
8	29.5§	23.3	22.9	20.9	21.4
9	45.0	≈29‡	38.6	36.1	32.5
10	137.5‡	147.3§	38.3	43.3	51.9
11	140.0	139.5	139.3	139.0	138.5
12	170.0	171.1	170.9	170.6	169.9
13	118.9	118.7	117.4	117.2	118.0
14	|	112.3	25.3	13.6	15.1
15	18.8	21.5§	24.3	113.4	22.6

δ in ppm (100 MHz, $CDCl_3$, 25°). Signals have been assigned by means of 2D-NMR experiments.

* At 58°. Signals from the acetate group: 170.0, 21.1.

† In $CDCl_3$–CD_3OD 3:1.

‡ Very low and broad.

§ Broadened.

¶ Obscured by the solvent signal.

‖ Not emerged from the background.

type [14] and explain the NOE between H-15 and H-1, which would otherwise be very difficult to understand. Conformation B, which is of the DD type, explains the existence of NOEs between H-15 and hydrogens H-2 and H-7. Conformations similar to these have been proposed to explain the cyclization of 1α-hydroxy germacranolides to *trans*-guaianolides [15].

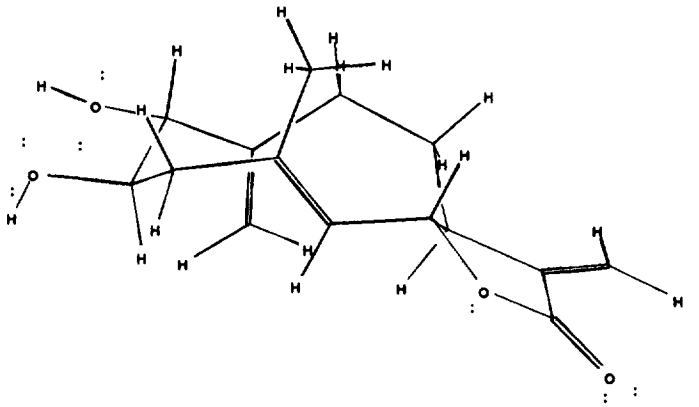
It is likely that lactone **2**, which we now would like to name lucentolide, has its biogenetic origin in **1a**. However, the α orientation of the hydroxyl group at C-1 has no precedent in naturally occurring germacr-10(14)-en-*trans*-12,6-olides. In all cases described thus far, both enzymatic and chemical oxygenations of the 1,10 double bond in precursors of the costunolide type take place from the β side and lead to β-oxygenated germacranolides [7, 16]. This is due to the fact that oxygenation occurs in a chair–chair (crown) conformation, in which this side is more accessible [14, 17, 18]. The structure of **2**, however, indicates that oxygenation took place from the α side. In order to find an explanation for this fact, we also carried out molecular mechanics calculations with the putative biosynthetic precursor **1a**. The results are displayed in Scheme 2. We have mentioned above that its acetate **1b** shows conformational mobility. In fact, as in the previous case, three conformations of close energy, A (UU), B (DD) and C (UD) [14], were found to be the main conformations of the molecule. This explains some NOEs which would not be easy to understand if only one conformation is taken into account. For instance, H-14 (methyl group at C-10) shows a NOE with H-6 (conformation A) but also with H-2 and H-5 (conformations B and C). In the same way, H-15 shows a NOE with H-6 (conformations A and C) and also with H-1 (conformation C). The second important aspect here is that enzymatic oxygenation of conformations B and C should take place from the now less hindered α-side of the C-1/C-10 double bond. This leads to α-oxygenated germacranolides and explains the formation of **2**.

Compound **5**, $C_{15}H_{18}O_2$, was a γ-lactone (IR ν_{max} 1768 cm^{-1}) which displayed an endocyclic conjugated diene fragment (UV λ_{max} 267 nm). No other functional group were present, as judged from the IR and NMR data (Tables 1 and 3). The latter indicated a gross structure identical with that of the known eudesmanolide gazaniolide [19, 20]. However, NOE measurements revealed a spatial proximity between H-14 and both H-1 and H-5, as well as between H-3 and H-15. Furthermore, no NOE was observed between H-6 and H-14. In view of these data, and taking into account the values of the coupling constants, we concluded that **5** is 10-*epi*gazaniolide, which has the unusual 10-*epi*eudesmane framework. Molecular mechanics calculations [12] showed a good agreement with the observed data and pointed out that alternative structures such as 5-*epi*gazaniolide or 5,6-*diepi*gazaniolide, while still explaining some NOEs, were not able to account for both the observed value of $J_{5,6}$ and the absence of a NOE between H-6 and H-14.

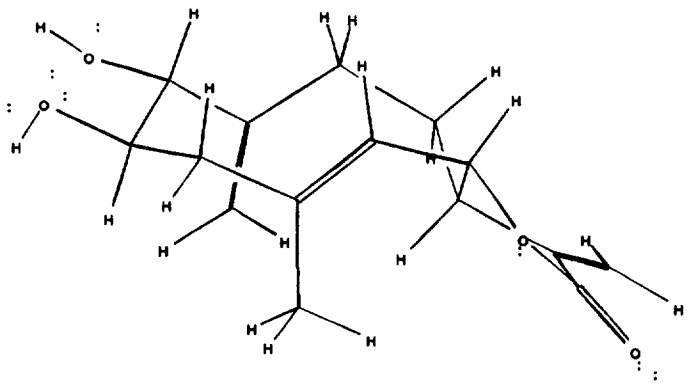
Compound **6** was a hydroxylated lactone (IR ν_{max} 3450, 1772 cm^{-1}). The NMR data (Tables 1 and 3) indicated the presence of a conjugated γ-lactone, two hydroxyl groups and a $C{=}CH_2$ group. The sharp three-proton singlet at δ 0.94 suggested a eudesmane system. Spin decoupling experiments established the presence of a C–CHOH–CHOH–CH_2–C(=CH_2) and a CH–CH(OR)–CH–CH_2–CH_2–C fragment. In view of this, only structure **6** was likely. The depicted configurations were deduced from the values of the coupling constants and supported by NOE measurements. For example, H-14 displayed a marked NOE with H-6, but none with either H-1 or H-2. Furthermore, H-1 showed a NOE with H-2 and H-5. Lactone **6** has its most probable biogenetic origin in the 1β,2β-dihydroxy germacranolide analogous to **2**. This compound, however, has not been detected in the present work.

Methyl ester **7** was found in a small amount in one of the polar fractions of the extract. Its spectral features (see Experimental), which were close to those of **6**, permitted its easy identification as the formal methanolysis product of the latter. As a matter of fact **7** does not show any particular tendency to extrude methanol with reversal back to **6**. Nevertheless, it remains questionable whether **7** is a true natural product or an artifact formed during the isolation procedure.

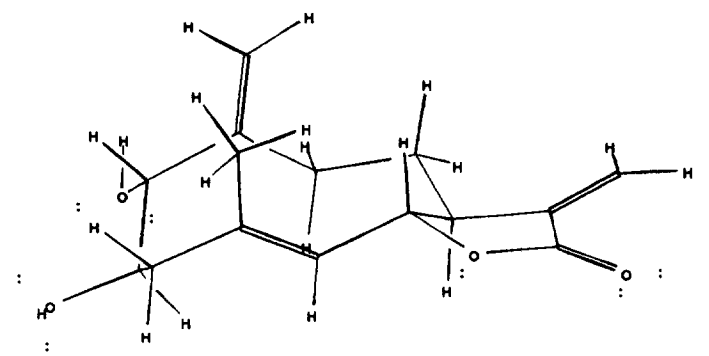
Compounds **9** and **10** had very close NMR data (Table 4), which suggested that their structures only differed in minor aspects. In part, their NMR spectra were similar to those of the bisaboloxide A derivative



Conformation A



Conformation B

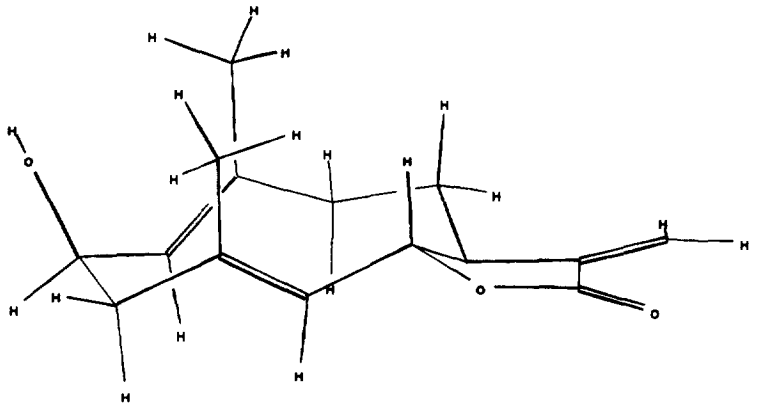


Conformation C

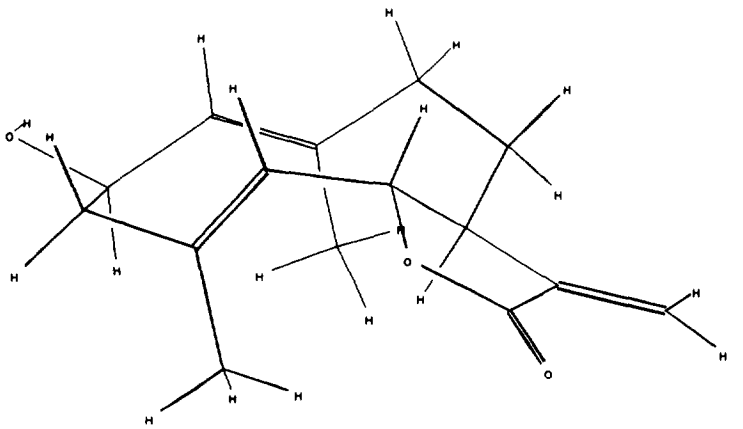
Scheme 1. Major conformations of germacranolide **2** as found by molecular mechanics calculations.

8, already found in the previous investigation [3]. However, in both compounds a *cis*-disubstituted C=C bond replaced the trisubstituted olefin and a ^{13}C NMR signal from a tertiary oxygenated carbon replaced that of the secondary allylic alcohol present in **8**. Only the allylic hydroperoxide **9** and the corresponding alcohol **10** were in agreement with these spectral features. Two-dimensional C,H-COSY experiments also supported this structural assignment. As definitive confirmation, the less polar of the two compounds, **9**, was converted into the other by treatment with dimethyl sulphide at room temperature.

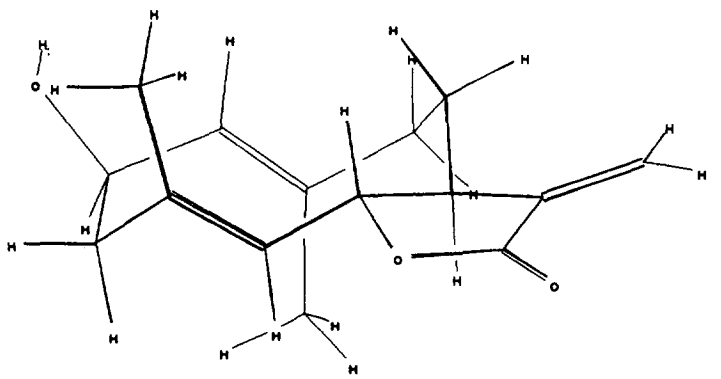
Compound **11** had NMR spectral features (Table 4) similar in part to those of **8**. Aside from the absence of an acetate group, the ^{13}C NMR signals had the



Conformation A



Conformation B



Conformation C

Scheme 2. Main conformations of germacranolide **1a** (**1b**), as found by molecular mechanics calculations.

same multiplicity as those of the latter compound, but also markedly different chemical shifts. Extensive spin decoupling experiments revealed the same hydrogen connectivities as in **8**. In view of this, only structure **11**, a derivative of bisabololoxide B, was likely. Comparison with the published ^{13}C NMR data of bisabololoxide B itself gave support to this structural attribution [21]. Both **8** and **11** may biogenetically arise through intramolecular attack of a hydroxy group to an epoxide ring in a monocyclic (−)-α-bisabolol derivative, a process which has already been described *in vitro* [21].

Table 4. ^1H and ^{13}C NMR data of bisabolenes **9**, **10** and **11**

H	9	10	11	C	9	10	11
1	**5.96** *ddd* (10; 2; 1.5)	5.80 *ddd* (10.5; 2; 1.5)	4.26 *br d* (8)	1	131.2	129.0	68.1
2	5.75 *ddd* (10; 2.5; 1.5)	5.66 *ddd* (10.5; 2.5; 1.5)	5.32 *br s*	2	134.3	135.5	124.6
4	1.85 *m*	1.90 *m**	2.05 *br t* (16)	3	67.1	69.8	135.9
	1.47 *m**	1.60 *m**	1.85 *m**				
5	1.75 *m**	1.85 *m**	1.70 *m**	4	37.4	38.7	30.4
	1.50 *m**	1.30 *m**	1.25 *m**				
6	2.07 *m**	2.20 *m*	1.74 *m*	5	19.8	22.4	24.4
8	1.75 *m**	1.65 *m**	1.90 *m**	6	48.1	48.1	49.8
	1.25 *m**	1.25 *m**	1.50 *m*				
9	1.75 *m**	1.75 *m**	1.94 *m**	7	75.0	75.0	87.6
	2.03 *br ddd*	2.00 *m*	1.90 *m**				
	(15; 5.5; 2.5)			8	24.5	24.9	31.7
10	4.71 *dd*	4.70 *dd*	3.83 *dd*	9	20.7	20.8	25.6
	(4; 2.5)	(4; 2.5)	(7.5; 6.5)	10	71.9	72.1	83.7
12	1.11 *s*	1.11 *s*	1.14 *s*†	11	72.8	72.8	71.3
13	1.30 *s*	1.28 *s*	1.23 *s*†	12	27.2	27.1	24.9†
14	1.24 *s*	1.18 *s*	1.24 *s*	13	27.7	27.8	25.7†
15	1.27 *s*	1.26 *s*	1.66 *br s*	14	24.6	24.1	27.3
OAc	2.08 *s*	2.08 *s*	—	15	29.6	28.1	22.9
				OAc	170.6/21.2	170.6/21.1	—

δ in ppm and J (parentheses) in Hz, 400 MHz (^1H) and 100 MHz (^{13}C), $CDCl_3$, 22°.

* Overlapped signal.

† The signal assignments of the two diasterotropic methyl groups are interchangeable.

The IR data of compound **12**, isolated in a very small amount, indicated the presence of a conjugated γ-lactone ring and an aldehyde group (ν_{max} 2706, 1770, 1731 cm^{-1}) and the absence of other functions. The ^1H NMR spectrum (Table 1) confirmed these conclusions and showed in addition signals from a methyl bound to a quaternary carbon (sharp three-proton singlet at δ 1.15) and from a isoproprenyl fragment. No mass spectrum could be measured since the compound decomposed in the ionization chamber, but the ^{13}C NMR spectrum (Table 3) showed the presence of only 14 carbon atoms, which suggested a norsesquiterpene derivative. Taking into consideration the signal multiplicities, a molecular formula $C_{14}H_{18}O_3$, with six unsaturations, was likely. Extensive decoupling experiments led finally to **12**, a 2-nor-elemanolide, as the only feasible structure. This conclusion is also supported by comparison with structurally related compounds [3, 11]. The values of the coupling constants and the observed NOEs (e.g. between H-1 and H-5) pointed unequivocally to the depicted stereochemistry. Compound **12** is formally derived from 11,13-dehydro saussurea lactone [7, 11] by oxidative cleavage of the C1–C2 olefinic bond.

Compound **13**, $C_{10}H_{16}O_2$, was a hydroxylated monoterpene ketone (IR ν_{max} 3450, 1730 cm^{-1}). No signals from olefinic carbon atoms were present in the ^{13}C NMR spectrum (Experimental), which further confirmed the presence of a ketone and a secondary alcohol group. The compound therefore was bicyclic. A combination of spin decoupling, NOE measurements and 2D H,C-COSY experiments led finally to the proposed structure, which corresponds to that of the 6-*endo*-hydroxy derivative of (+)-camphor. A perusal of the literature pointed out that the compound had previously been prepared via chemical [22] and biochemical methods [23], but never isolated as a natural product.

Compound **14** has previously been described [10]. Since only low-resolved ^1H NMR data were given, we now report the complete ^{13}C NMR and high-resolution ^1H NMR data (Experimental). The *trans* stereoisomer has also been isolated from natural sources [10, 24].

EXPERIMENTAL

NMR: 400 MHz (^1H) and 100 MHz (^{13}C) in $CDCl_3$ (at 22° unless otherwise stated). NOE measurements were carried out by the one-dimensional difference method. Optical rotations at 22°. MPCC: silica gel Merck (particle size 25–40 μ), gradient elution with the solvent mixts indicated in each case. HPLC: LiChrosorb RP-8 (250 × 8 mm), elution with MeOH–H_2O mixts.

Plant material. Aerial parts of *A. lucentica* were collected in June 1993, in the same geographical location as in the previous work [2, 3]. A voucher specimen (BCF-38108) 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 (900 g of aerial parts) was processed according to the described protocol [25]. The defatted extract was prefractionated by CC on silica gel (fr. A, hexane–EtOAc 3:1; fr. B, hexane–EtOAc 1:1; and fr. C, EtOAc–MeOH 9:1). The three frs were subjected to further chromatographic sepns, firstly by MPCC (eluents indicated in parentheses) and then by either prep. TLC or HPLC.

Fr. A (hexane–*t*BuOMe 15:1 → 3:1) afforded several previously isolated compounds [2, 3] together with **1b** (9 mg), **3** (8 mg), **5** (22 mg), **8** (15 mg), **9** (8 mg), **10** (15 mg), **11** (20 mg), **12** (3 mg), **13** (30 mg), **14** (6 mg) and deacetoxymatricarin (28 mg).

Fr. B (CH_2Cl_2–MeOH 50:1 → 25:1) afforded compound **4** (13 mg), as well as previously isolated compounds [2, 3].

Fr. C (CH_2Cl_2–MeOH 50:1 → 5:1) afforded previously isolated compounds [2, 3] and, in addition, compounds **2** (4 mg), **6** (5 mg), **7** (5 mg), artecanin (4 mg), 1β-hydroxyarbusculin A (23 mg), and *iso-seco*tanapartholide (33 mg).

2β-Acetoxycostunolide (**1**). Oil, $[\alpha]_D$ +24° ($CHCl_3$; *c* 1); IR ν_{max}^{film} cm^{-1}: 1760 (lactone C=O), 1735 (ester C=O), 1440, 1370, 1240, 1140, 1025, 975, 945; EIMS (probe) *m/z* (rel. int.): 230.1318 $[M-HOAc]^+$ (100), 215 $[M-HOAc-Me]^+$ (51), 185 (24), 175 (27), 159 (32), 147 (45), 119 (56), 105 (51), 84 (66), 67 (39), 56 (62). Calc. for $C_{17}H_{22}O_4$–HOAc, M = 230.1306; NMR: Tables 1 and 3.

Lucentolide (**2**). Mp, IR and MS data have been previously reported [3]; NMR: Tables 2 and 3.

10-epi*Gazaniolide* (**5**). Oil, $[\alpha]_D$ +214° ($CHCl_3$, *c* 0.4); IR ν_{max}^{film} cm^{-1}: 3026, 1768 (lactone C=O), 1733sh, 1673, 1650, 1449, 1403, 1343, 1243, 1187, 1152, 1127, 1041, 1024, 977, 958, 814, 728; UV λ_{max}^{EtOH} nm: 267; EIMS (probe) *m/z* (rel. int.): 230.1320 $[M]^+$ (43), 215 $[M-Me]^+$ (38), 149 (100), 119 (32), 105 (42), 91 (26), 58 (30). Calcd for $C_{15}H_{18}O_2$, M = 230.1306; NMR: Tables 1 and 3.

1β,2β-Dihydroxy-5α,6β,7αH-eudesma-4(15),11(13)-dien-12,6-olide (**6**). Oil, $[\alpha]_D$ +55° ($CHCl_3$; *c* 1); IR ν_{max}^{film} cm^{-1}. 3450 (br, OH), 1772 (lactone C=O), 1740sh, 1460, 1265, 1135, 1095, 1030, 985, 945; EIMS (probe) *m/z* (rel. int.): 264.1349 $[M]^+$ (6), 246 $[M-H_2O]^+$ (100), 228 $[M-2H_2O]^+$ (14), 203 (15), 189 (16), 163 (25), 105 (24), 95 (32), 91 (28). Calcd for $C_{15}H_{20}O_4$, M = 264.1361; NMR: Tables 1 and 3.

Methyl 1β,2β,6α-trihydroxy-5α,7αH-eudesma-4(15),11(13)-dien-12-oate (**7**). Oil, $[\alpha]_D$ +7.5° ($CHCl_3$; *c* 1.6); IR ν_{max}^{film} cm^{-1}: 3450 (br, OH), 1725 (*br*, ester C=O), 1660, 1635, 1450, 1400, 1275, 1245, 1165, 1055, 1020, 1000, 955, 910, 895, 820, 740; EIMS (probe) *m/z* (rel. int.): 296.1629 $[M]^+$ (12), 278 $[M-H_2O]^+$ (29), 264 $[M-MeOH]^+$ (16), 260 $[M-2H_2O]^+$ (22), 246 $[M-H_2O-MeOH]^+$ (24), 232 (26), 218 (34), 200 (36), 189 (33), 173 (32), 161 (46), 143 (41), 133 (45), 123 (100), 105 (56), 95 (70), 81 (42), 69 (36). Calcd for $C_{16}H_{24}O_5$, M = 296.1623; ^1H NMR (400 MHz, $CDCl_3$, 22°): δ 6.28 (1H, *br s*; H-13), 5.72 (1H, *br s*; H-13′), 5.15 (1H, *br s*; H-15), 4.92 (1H, *br s*; H-15′), 4.07 (1H, *ddd*, *J* = 3.5, 2.5 and 2 Hz; H-2), 4.02 (1H, *t*, *J* = 10 Hz; H-6), 3.76 (3H, *s*; OMe), 3.34 (1H, *br d*, *J* = 3.5 Hz; H-1), 2.56 (1H, *ddd*, *J* = 12, 10 and 5 Hz; H-7), 2.49 (1H, *dd*, *J* = 14 and 2.5 Hz; H-3β), 2.40 (1H, *br ddd*, *J* = 14, 2.5 and 2 Hz; H-3α), 1.96 (1H, *ddd*, *J* = 13, 3.5 and 3.5 Hz; H-9β), 1.87 (1H, *br d*, *J* = 10 Hz; H-5), 1.70 (1H, *dddd*, *J* = 14, 13, 12 and 3.5 Hz; H-8β), 1.65 (1H, *overlapped m*; H-8α), 1.27 (1H, *br ddd*, *J* = 13, 13 and 5 Hz; H-9α); ^{13}C NMR (100 MHz, $CDCl_3$, 22°): δ (consecutively from C-1 to C-15 and OMe) 79.1, 71.5, 42.6, 141.0, 55.9, 68.8, 47.6, 25.8, 36.6, 42.3, 142.4, 168.0, 125.2, 13.4, 111.5, 52.0.

(3S,6S)-3-*Acetoxy*-2,2,6-*trimethyl*-6-([1S,4R]-4-*hydroperoxy*-4-*methylcyclohex*-2-*en*-1-*yl*)*tetrahydropyran* (**9**). Oil, $[\alpha]_D$ +9.5° ($CHCl_3$; *c* 1); IR ν_{max}^{film} cm^{-1}: 3400 (br, OH), 1730 (acetate C=O), 1450, 1370, 1240, 1210, 1105, 1055, 1010, 985, 900, 730; EIMS (probe) *m/z* (rel. int.): 279.1970 (8), 263 (12), 236 $[M-HO_2]^+$ (10), 203 (6), 186 (38), 185 (98), 143 (95), 125 (100), 107 (45), 93 (24), 83 (28), 71 (44), 56 (65). Calc. for $C_{17}H_{28}O_5$–HO_2, M = 279.1960; NMR: Table 4 (the name above corresponds to IUPAC rules but the structural formula in the scheme displays the usual atom numbering of the bisabolene framework).

(3S,6S)-3-*Acetoxy*-2,26-*trimethyl*-6-([1S,4R]-4-*hydroxy*-4-*methylcyclohex*-2-*en*-1-*yl*)*tetrahydropyran* (**10**). Oil, $[\alpha]_D$ + 5.5° ($CHCl_3$; *c* 1.5); IR ν_{max}^{film} cm^{-1}: 3400 (br, OH), 1735 (acetate C=O), 1440, 1370, 1250, 1110, 1025, 980, 900, 815, 795, 730; EIMS (probe) *m/z* (rel. int.): 278.1895 $[M-H_2O]^+$ (1), 263 $[M-H_2O-Me]^+$ (1), 236 $[M-HOAc]^+$ (2), 203 $[M-H_2O-Me-HOAc]^+$ (4), 186 (17), 185 (100), 143 (85), 125 (96), 107 (26), 97 (30), 83 (35), 71 (46), 56 (42). Calcd for $C_{17}H_{28}O_4$–H_2O, M = 278.1882; NMR: Table 4 (the name above corresponds to IUPAC rules, but the structural formula in the scheme displays the usual atom numbering of the bisabolene framework).

(1R)-1-*Hydroxybisabololoxide B* (**11**). Oil, $[\alpha]_D$ −18.5° ($CHCl_3$; *c* 4.8); IR ν_{max}^{film} cm^{-1}: 3400 (br, OH); EIMS (probe) *m/z* (rel. int.): 236.1770 $[M-H_2O]^+$ (1), 221 $[M-H_2O-Me]^+$ (2), 193 (41), 143 (100), 125 (56), 109 (52), 101 (80), 93 (64), 83 (68), 71 (77), 56 (86). Calc. for $C_{15}H_{26}O_3$–H_2O, M = 236.1776; NMR: Table 4.

1-*Oxo*-5α,6β,7αH-2-*norelema*-3,11(13)-*dien*-12,6-*olide* (**12**). Oil, $[\alpha]_D$ +44° ($CHCl_3$; *c* 0.2); IR ν_{max}^{film} cm^{-1}: 3082, 2706, 1770 (lactone C=O), 1731 (aldehyde C=O), 1454, 1403, 1378, 1250, 1120, 903, 737; EIMS: sample decomposition; NMR: Tables 1 and 3.

(1S,4R,6R)-6-*Hydroxy*-1,7,7-*trimethylbicyclo*[2.2.1]*heptan*-2-*one* (6-*endo*-*hydroxycamphor*) (**13**). Oil, $[\alpha]_D$ +19° ($CHCl_3$; *c* 0.75); IR ν_{max}^{film} cm^{-1}: 3450 (br, OH), 3060, 1730 (ketone C=O), 1450, 1415, 1390, 1375, 1260, 1145, 1070, 1040, 1005, 910, 890, 735; EIMS (probe) *m/z* (rel. int.): 168.1161 $[M]^+$ (8), 153 $[M-Me]^+$ (62), 135 $[M-H_2O-Me]^+$ (16), 111 (38), 109 (46), 108 (100), 107 (96), 93 (84), 81 (34), 69 (37), 56 (51). Calcd. for $C_{10}H_{16}O_2$, M = 168.1150; ^1H NMR (400 MHz, $CDCl_3$, 22°): δ 4.16 (1H, *br dd*, *J* = 10 and

2.5 Hz; H-6), 2.54 (1H, *dddd*, J = 13.5, 10, 4.5 and 3 Hz; H-5_{exo}), 2.43 (1H, *ddd*, J = 18.5, 5 and 3 Hz; H-3_{exo}), 2.14 (1H, *br dd*, J = 5 and 4.5 Hz; H-4), 1.98 (1H, *d*, J = 18.5 Hz; H-3_{endo}), 1.33 (1H, *dd*, J = 13.5 and 2.5 Hz; H-5_{endo}), 0.96 (6H, *s*; two Me groups on C-1 and C-7), 0.82 (3H, *s*; Me group on C-7); ^{13}C NMR (100 MHz, $CDCl_3$, 22°): δ (consecutively from C-1 to C-7 and the three methyl groups) 63.8, 216.7, 43.5, 41.5, 37.7, 75.9, 48.7, 7.3 (Me on C-1), 20.7, 19.8 (2 Me on C-7) (name and atom numbering correspond on IUPAC rules).

(4R,5S)-4-*Hydroxy*-5-*isopropyl*-2-*methyl*-2-*cyclohexehone* (**4**). Oil, $[\alpha]_D$ +81° ($CHCl_3$; *c* 0.6); ^{1}H NMR (400 MHz, $CDCl_3$, 22°): δ 6.77 (1H, *dq*, J = 5.5 and 1.5 Hz; H-3), 4.40 (1H, *br dd*, J = 5.5 and 3 Hz; H-4), 2.55 (1H, *dd*, J = 16.5 and 4 Hz; H-6), 2.44 (1H, *dd*, J = 16.5 and 2.5 Hz; H-6′), 1.79 (3H, *br s*; Me on C-2), 1.76 (1H, *m*; *iso*propyl CH), 1.65 (1H, *m*; H-5), 1.02, 0.95 (3H each, *d*, J = 6.5 Hz; *iso*propyl Me); ^{13}C NMR (100 MHz, $CDCl_3$, 22°C): δ (consecutively from C-1 to C-6 and then the substituents) 200.2, 137.2, 142.9, 64.2, 45.9, 36.9, 15.6 (Me on C-2), 28.5 (*iso*propyl *C*H), 20.4, 20.3 (2 × *iso*propyl Me) (name and atom numbering correspond to IUPAC rules).

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