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SESQUITERPENE LACTONES FROM *ARTEMISIA HERBA-ALBA* SUBSP. *HERBA-ALBA*

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Key Word Index—*Artemisia herba-alba* subsp. *herba-alba*; Compositae; Anthemideae; sesquiterpene lactones; germacranolides; eudesmanolides.

Abstract—Extraction of aerial parts of *Artemisia herba-alba* subsp. *herba-alba* and chromatographic separation yielded, in addition to known compounds, three new germacranolides and four new eudesmanolides. The question about the structures of artesin and its 11-epimer is discussed.

INTRODUCTION

Artemisia herba-alba Asso subsp. *herba-alba* (= *A. aragonensis* Lam.), one of two subspecies of *A. herba-alba* Asso growing in Spain, is a small shrub with grey-greenish leaves and a very weak aromatic odour [1]. It is relatively abundant in north-east Spain, particularly in the Aragonese country. Although several papers have been published on the chemical composition of specimens of *A. herba-alba* growing in Egypt and Israel [2], nothing is known about the metabolites of this Spanish subspecies. In the present publication, the results in the investigation of the terpenoid metabolites of *A. herba-alba* subsp. *herba-alba* are presented. Three new germacranolides **2**, **7**, **8** and four new eudesmanolides **10**, **12**, **16** and **18** were isolated from aerial parts of the plant. In addition to these new lactones, the known compounds **1** [3], gallicin (**3**) [4], 11-epigallicin (**4**) [5], **5** [6], shonachalin A (**6**) [6, 7], 11β,13-dihydroreynosin (**9**), artesin (**11**) [8] (see below), erivanin (**13**) [9], artemin (**14**) [10], taurin (**15**) [11], **17** [6, 12], artapshin (**19**) [12, 13], the monoterpene diol **20** [14] and scopoletin (**21**) were also found.

RESULTS AND DISCUSSION

Compound **2** was a sesquiterpene ketolactone according to its IR bands (1789, 1682 cm^{-1}) and molecular formula $C_{15}H_{20}O_3$ (M^+ at m/z 248). The ^1H NMR spectrum in $CDCl_3$ at room temperature displayed very broad signals, as usually observed in molecules with slow conformational interconversions [15, 16]. For this reason, the spectrum was measured in C_6D_6 at high temperature, where the conformational interconversions became fast enough to yield sharp NMR spectra (see Table 1). The signals were typical of a germacranolide with two double bonds at $\Delta^{10(14)}$ (broad singlet at δ5.21 and doublet at 5.05) and Δ^5 (broad doublet at 4.87), the former conjugated with a keto group. The triplet at δ4.25 (J = 10 Hz) obviously came from the lactone proton. The position and shape of the signal suggested a *trans*-germacran-12,6-olide. The spectrum displayed marked similarities to that of **1** (Table 1), the main exception being the aspect of the signal of H-11, which appeared as a quintuplet (J = 7.5 Hz) at δ2.22, rather than as a double quartet at 1.67 (J = 12, 7 Hz). The downfield shift and decrease in the value of the coupling constant $J_{7,11}$ clearly indicated **2** to be the 11-epimer of **1** [17]. This conclusion could be confirmed by decoupling experiments. Other signals which undergo marked downfield shifts in **2** with respect to **1** are those of H-6 and H-7, whereas H-13 experiences an upfield shift.

A similar reasoning served to assign the structure of compound **7**. The IR spectrum pointed to the presence of hydroxyl and lactone functions. As with compound **2**, the aspect of the NMR spectrum suggested a *trans*-germacran-12,6-olide structure with double bonds at Δ^4 and $\Delta^{10,14}$. The spectrum in C_6D_6 at 75° was very similar to that of **6** (shonachalin A) with the exception of the signals of H-6, H-7, H-8 and H-11 (Table 1), which appeared shifted downfield, and that of H-13, which moved upfield. Moreover, the signal of H-11 was now a quintuplet ($J_{7,11} = J_{11,13} = 7.5$ Hz). According to this [17], compound **7** is 11-*epi*shonachalin A.

Compound **8**, isolated in a very small amount as an unstable oil, was an hydroperoxide, as deduced from the broad singlet at *ca* δ8 in the ^1H NMR spectrum. In view of the general similarities of this NMR spectrum with that of **6**, structure **8** appeared reasonable for the compound. The double doublet at δ4.12 (J = 11, 3 Hz) was thus assigned to the proton next to the hydroperoxide, as the signal is shifted downfield in comparison with the corresponding signal of H-1 in **6** (Table 1). As a confirmation of the structure, reduction of compound **8** with triphenylphosphine yielded **6**. Moreover, reaction with acetic anhydride gave **5a**, the acetylated derivative of **5** (see Experimental).

Compound **10** was an eudesmanolide, according to the ^1H NMR spectrum (Table 2). The sharp singlet at δ0.82, the two broad singlets at 4.98 and 4.84, the lactone triplet at 4.27 (J = 11 Hz) and the double doublet at 3.51 (J = 11.5, 4.5 Hz) strongly suggested a structure related to **9** (11β,13-dihydroreynosin), a compound which can be

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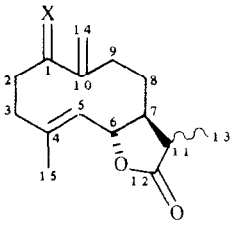
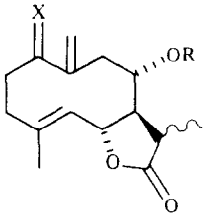
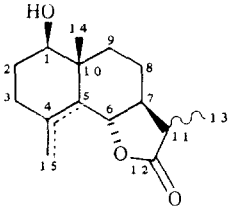


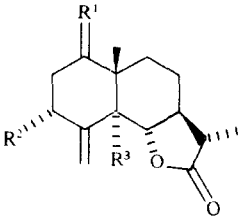
1 X = O (11βH)
2 X = O (11αH)
3 X = H, βOH (11βH)
4 X = H, βOH (11αH)



5 X = O R = H (11βH)
5a X = O R = Ac (11βH)
6 X = H, βOH R = H (11βH)
7 X = H, βOH R = H (11αH)
8 X = H, βOOH R = H (11βH)



9 $\Delta^{4(15)}$ (11βH)
10 $\Delta^{4(15)}$ (11αH)
11 Δ^{4} (11βH)
12 Δ^{4} (11αH)

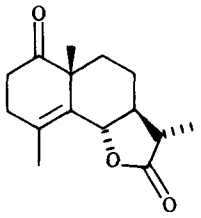


13 R¹ = H, αOH R² = OH R³ = H
14 R¹ = H, βOH R² = H R³ = OH

obtained from reynosin [18] by reduction with sodium borohydride. The principal difference lies in the position and shape of the H-11 signal (quintuplet at δ2.65, J = 7.5 Hz), as well as in the positions of the signals from H-6 and H-7, all of them shifted markedly downfield (Table 2). As in the cases discussed above, these changes can be explained by an inversion in the stereochemistry of C-11, i.e. compound **10** is 11α,13-dihydroreynosin. Another support of this structural assignment is the position of the signal of C-13 (δ9.68) in the ^{13}C NMR spectrum (Table 3), a typical value in eudesmanolides with β-Me groups at C-11. An α-Me group would be expected to give this signal above 11 ppm [19]. Compound **10** was described as forming during gas chromatography of compound **4** [5]. The authors also pointed out, from comparison of NMR data, that the 11,13-dihydroderivative of reynosin isolated 10 years ago in our laboratory from *A. herba-alba* subsp. *valentina* [20] was probably **10**, not **9**. A direct comparison of the compounds has now shown that compound **10** was actually isolated in that time but, unfortunately, we overlooked the true stereochemistry at C-11.

Compound **12**, mp 126–127°, also displayed characteristic NMR spectral features of a *trans*-eudesman-12,6-olide. The lactone proton appeared here as a doublet at δ4.80, split by several small, long-range couplings, a pattern very similar to that observed in the NMR spectrum of compound **11** (Table 2). However, appreciable downfield shifts in the signals of H-6, H-7 and H-11 are observed in the spectrum of **12**, as well as a decrease in the coupling constant $J_{7,11}$ (from 12 Hz in **11** to 7.5 Hz in **12**). Here again, the most evident conclusion is that **12** is the 11-epimer of compound **11**. The ^{13}C NMR signal of C-13 at δ9.81 (Table 3) lends firm support [19] to this structural attribution.

A careful examination of the literature revealed that no compound with the spectral properties of **12** has been described up to now. Seventeen years ago, a sesquiterpene lactone with this structure but with undefined stereochemistry at C-11, named artesin (mp 172°), was reported in *A. santolina* [8]. Furthermore, the authors found that the compound gave taurin, of unknown C-11 stereochemistry at that time, upon oxidation with Jones reagent. Unfortunately, the summary of ref. [8] in the Chemical Abstracts erroneously reported the structure of artesin to be **12** (β-Me at C-11). Nine years later [11], it was confirmed that both taurin and artesin had an α-Me group at C-11 (11βH configuration), i.e. artesin had structure **11**. In the meantime, compound **11** (mp. 177°) had been found in *A. granatensis* [21] and several times since then in other plant sources. In 1986, structure **12** was assigned to a product isolated from *A. caerulescens*



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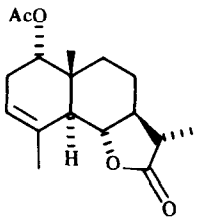

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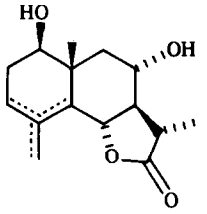
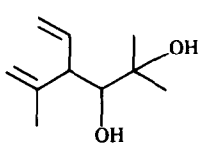
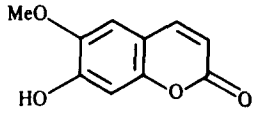


17 Δ^3
18 Δ^4
18a Δ^4, ketone at C-1
19 $\Delta^{4(15)}$



20



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subsp. *gallica* [22] but the authors did not give any spectral nor physical data and referred again to the paper in ref. [8], which actually contains the data of **11**. In this communication, the true physical and spectral data of **12**, which has to be named as 11-*epi*artesin, are thus given for the first time.

Compound **16** was isolated in a very small amount and its structure relies thus practically only on a NMR spectrum. Whereas the spectrum displayed some analogies to those of eudesmanolides **9** and **11** (lactone double doublet at δ3.95, sharp singlet from the angular methyl group at 0.93), the double doublet at *ca* 3.5 of the latter compounds was here replaced by a broad doublet at 4.63 ($J = ca$ 4.5 Hz). As the product had an acetate residue (singlet at δ2.08), the doublet probably originated in the proton next to an acetylated secondary alcohol. The shape of the signal and the small value of the coupling constant could be explained by assuming a 1α-acetoxyl group [22, 23]. Furthermore, the broadened olefinic singlet at δ5.29 and the broad methyl singlet at 1.86 indicated the presence of a Δ^3-double bond. This was confirmed by decoupling experiments. Irradiation at, respectively, δ5.29 and 4.63 eliminated in each case a small long-range coupling, thus sharpening the corresponding signals. These irradiations also affected two broad multiplets at δ2.43 and 2.07, which were assigned to the protons at C-2. The compound did not give a molecular peak in the mass spectrum but instead a $[M - HOAc]^+$ base peak. Structure **16** corresponds to the acetylated derivative of 11β,13-dihydrodouglanin [24].

The more polar fractions contained the dihydroxylated lactones **17**–**19**. Lactone **18** was isolated as a mixture with **17**, which proved impracticably difficult to separate, in view of the small amount available. The NMR spectrum of the mixture contained signals which could be easily attributed to lactone **17** [6] and, in addition, several others which seemed to come from a closely related isomer. The appearance of a broad doublet at δ4.56 with a similar shape to the signal of H-6 in **11** pointed to an analogous eudesmanolide structure with a Δ^4-double bond and, like compounds **17** and **19**, a second hydroxy group at C-8α (double triplet at δ3.95). Confirmation of the structure was reached by synthesis of **18** by reduction of **18a** with sodium borohydride [25] (see Experimental). The physical and spectral data given in this paper are those of the synthetic product.

Two diastereoisomers with structure **20** were isolated four years ago from aerial parts of *Achillea filipendulina* [14]. According to the NMR spectral data, compound **20** is one of these stereoisomers. The absolute configuration, however, has not been determined.

EXPERIMENTAL

^{13}C NMR spectra were measured at 50 MHz. IR spectra were measured in solution (CCl_4) or as a KBr pellet (compound **18**). HPLC was performed in the reverse phase mode on LiChrosorb RP-8 or RP-18 columns (250 × 8 mm, detection by refractive index). MPLC was carried out at 10 bar head pressure in a glass column filled with Woelm silica gel (30–60 μ). TLC (silica gel) was on Merck plates.

Plant material. Aerial parts of *A. herba-alba* subsp. *herba-alba* were collected in the vicinity of Arcos de las Salinas (Teruel, Spain) in November 1987 and authenticated by Dr A. Aguilella, from the Department of Botany at the Faculty of Biology (University of Valencia, Spain). A voucher specimen has been deposited in the herbarium of this Department.

Extraction and chromatography. The air-dried plant material (600 g) was extracted at room temp. with hexane–Et_2O–MeOH (1 : 1 : 1) (10 l. 5 days) [26]. The extract (22 g) was defatted by pptn from MeOH in the cold and then prefractionated by CC on silica gel. Seven fractions were collected after elution with hexane, 10, 25, 50 and 75% Et_2O in hexane, Et_2O and 20% MeOH in Et_2O respectively. The fractions corresponding to elution in the range hexane–25% Et_2O in hexane (*ca* 7 g overall) contained mainly waxes, essential oils and sterols, and were discarded.

The fractions obtained from the elution with 50 and 75% Et_2O in hexane had a similar aspect in TLC and NMR and were thus mixed. The resulting fraction A (3.3 g) was submitted to medium pressure liquid chromatography (MPLC) on a silica gel column (55 × 2.5 cm). Elution was begun with 10% Et_2O in hexane (fractions of 20 ml). The composition of the solvent was

Table 1. ^{1}H NMR data of germacranolides **1**, **2**, **5**, **5a**, **6**, 7 and **8***

H	1	2	5†	5a†	6	7	8†
1	—	—	—	—	3.55 *dd*	3.55 *m*	4.12 *dd*
2α	2.60 *m*	2.59 *m*	2.77 *ddd*	2.61 *ddd*	1.65 *m*	1.65 *m*	2.09 *dddd*
2β	2.25 *m*	2.25 *m*	2.89 *ddd*	3.03 *ddd*			1.92 *dddd*
3α			2.55 *ddd*	2.53 *ddd*			
3β	1.90 *m*	1.89 *m*	2.35 *ddd*	2.35 *ddd*	1.85 *m*	1.85 *m*	2.25 *m*
5	4.85 *br d*	4.87 *br d*	5.00 *br d*	5.01 *br d*	4.89 *br d*	4.91 *br d*	5.21 *br d*
6	3.93 *t*	4.25 *t*	4.38 *t*	4.50 *t*	3.95 *t*	4.35 *t*	4.35 *t*
7	1.25 *m*	1.63 *m*	1.92 *ddd*	2.09 *ddd*	1.85 *m*	2.15 *m*	2.07 *m*
8α	1.40 *m*	1.35 *m*	—	—	—	—	—
8β	0.95 *m*	0.95 *m*	3.70 *ddd*	4.79 *ddd*	3.31 *br t*	3.55 *m*	3.88 *br t*
9α	2.15 *ddd*	2.14 *ddd*	}	2.77 *ddd*	1.85 *m*	1.85 *m*	2.33 *dd*
9β	2.20 *m*	2.20 *m*	} 2.65 *br m*	2.57 *dddd*	2.12 *m*	2.15 *m*	2.70 *br d*
11	1.67 *dq*	2.22 *dq*	}	2.41 *dq*	2.15 *dq*	2.69 *dq*	2.57 *dq*
13	1.03 *d*	0.86 *d*	1.41 *d*	1.36 *d*	1.46 *d*	1.14 *d*	1.45 *d*
14	5.22 *br s*	5.21 *br s*	5.81 *br s*	5.90 *d*	4.90 *d*	4.88 *br s*	5.25 *d*
	5.06 *d*	5.05 *d*	5.74 *d*	5.84 *dd*	4.79 *br s*	4.71 *br s*	5.22 *d*
15	1.40 *d*	1.38 *d*	1.73 *d*	1.77 *d*	1.38 *d*	1.38 *br s*	1.65 *d*
Other signals	—	—	—	2.10 *s* (OAc)	—	—	7.67 *br s* (OOH)

*At 400 MHz in C_6D_6 (75°).

†In $CDCl_3$ (57°).

Coupling constants in Hz: **1** $J_{5,6} = J_{6,7} = 10$; $J_{5,15} = 1.5$; $J_{8\alpha,9\alpha} = 2.5$; $J_{8\beta,9\alpha} = 11$; $J_{9\alpha,9\beta} = 14$; $J_{9,14'} = 1.5$; $J_{7,11} = 12$; $J_{11,13} = 7$. **2** $J_{5,6} = J_{6,7} = 10$; $J_{5,15} = 1.5$; $J_{8\alpha,9\alpha} = 2.5$; $J_{8\beta,9\alpha} = 11$; $J_{9\alpha,9\beta} = 14$; $J_{9,14'} = 1.5$; $J_{7,11} = J_{11,13} = 7.5$. **5** $J_{2,3\beta} = 6.5$; $J_{2',3\beta} = 4$; $J_{3\alpha,3\beta} = 12.5$; $J_{5,6} = J_{6,7} = 10$; $J_{5',15} = 1.5$; $J_{7,8} = 7.5$; $J_{8,9\alpha} = 9$; $J_{8,9\beta} = 3.5$; $J_{7,11} = 12$; $J_{11,13} = 7$; $J_{9,14'} = 1.5$. **5a** $J_{2\alpha,2\beta} = 11.5$; $J_{2\alpha,3\alpha} = 6$; $J_{2\alpha,3\beta} = 3.5$; $J_{2\beta,3\alpha} = 12.5$; $J_{2\beta,3\beta} = 6$; $J_{3\alpha,3\beta} = 12.5$; $J_{5,15} = 1.5$; $J_{5,6} = J_{6,7} = 10$; $J_{7,8} = 8$; $J_{7,11} = 11.5$; $J_{8,9\alpha} = 10$; $J_{8,8\beta} = 2.5$; $J_{9\alpha,9\beta} = 14.5$; $J_{9\alpha,14} = 1$; $J_{9\beta,14} = 1.5$; $J_{9\beta,14'} = 2$; $J_{11,13} = 7$. **6** $J_{1,2\alpha} = 4$; $J_{1,2\beta} = 9$; $J_{5,15} = 1$; $J_{5,6} = J_{6,7} = 10$; $J_{7,11} = 12$; $J_{11,13} = 7$; $J_{8,9(9')} = ca.\ 9$; $J_{9\alpha,9\beta} = 16$; $J_{9,14} = 1.5$. **7** $J_{5,6} = J_{6,7} = 10$; $J_{7,11} = J_{11,13} = 7.5$. **8** $J_{1,2\alpha} = 3$; $J_{1,2\beta} = 11$; $J_{2\alpha,2\beta} = 14$; $J_{2\alpha,3\alpha} = J_{2\alpha,3\beta} = 5$; $J_{5,6} = J_{6,7} = 10$; $J_{5,15} = 1.5$; $J_{7,11} = 11.5$; $J_{11,13} = 7$; $J_{7,8} = J_{8,9\alpha} = ca.\ 8.5$; $J_{8,9\beta} = J_{9,14} = J_{9,14'} = ca.\ 2$; $J_{9\alpha,9\beta} = 16$.

then progressively changed to Et_2O and 20% MeOH in Et_2O. After inspection by TLC and NMR, 6 fractions were collected. Fraction A-1 contained mainly sterols and was discarded. Fraction A-2 was submitted to HPLC (RP-8, MeOH–H_2O; 6:4, *ca* 130 bar). This gave **16** (1 mg) and **20** (5 mg). Fraction A-3 was fractionated by HPLC (RP-18, MeOH–H_2O, 3:2 *ca* 150 bar) and then prep. TLC (hexane–Et_2O, 1:1), giving **15** (2 mg) and more **20** (2 mg). Fraction A-4 was a mixture of the epimers **11** and **12**. Separation took place by prep. TLC (hexane–Et_2O, 1:2). This gave **11** (7 mg) and **12** (4 mg). Fraction A-5 was also a mixture of two epimers, **1** and **2**. Prep. TLC (hexane–Et_2O, 1:2) gave **1** (2 mg) and **2** (2 mg). Fraction A-6 was rechromatographed by HPLC (RP-18, MeOH–H_2O, 1:1, *ca* 165 bar). This gave **14** (20 mg) and a complex fraction which contained, in addition to **13** (1 mg), a mixture of lactone hydroperoxides which could not be characterized because of their rapid decomposition.

Fraction B (0.7 g) contained the material eluted with Et_2O. MPLC of this fraction (35 cm × 1.5 cm) was performed starting with hexane–Et_2O (1:1) and then increasing the polarity to Et_2O. Two main fractions, B-1 and B-2, were selected after inspection by NMR. Fraction B-1 was fractionated by HPLC (RP-18, MeOH–H_2O, 3:2, *ca* 150 bar). This gave more **14** (5 mg) and a mixture of the epimers **9** and **10**. Prep. TLC of this mixture (hexane–Et_2O, 1:2) gave **9** (5 mg) and **10** (6 mg). Fraction B-2 was submitted to prep. TLC (Et_2O), affording the separation of **3** (10 mg) and **4** (2 mg).

Fraction C (elution with 20% MeOH in Et_2O) weighed 2.4 g. Fractionation with MPLC [40 cm × 2.5 cm; elution with hexane–Et_2O (1:3) to Et_2O–MeOH (4:1)] gave three main fractions, C-1 to C-3 (inspection by TLC). Fraction C-1 was submitted to HPLC (RP-8, MeOH–H_2O, 1:1, 140 bar). This gave more **4** (5 mg) and a mixture of scopoletin **21** and the germacranolides **5** and **8**. Prep. TLC (2% MeOH in Et_2O) enabled the separation of **21** (2 mg) but still gave a mixture of **5** and **8**. Reaction of this mixture with Ac_2O gave **5a** (3 mg), which could be compared with an authentic sample, prepared by acetylation of **5** [6]. Fraction C-2 was fractionated by HPLC under the same conditions as C-1. This gave more **8** (2 mg) and an inseparable mixture of **17** and **18** (8 mg). Fraction C-3 was rechromatographed by HPLC (same conditions as before) and prep. TLC (5% MeOH in Et_2O). This gave **19** (8 mg), **6** (10 mg) and **7** (4 mg).

Compounds **3**, **5**, **6**, **9**, **13**–**15**, **17** and **19**–**21** could be compared with authentic samples (samples of compounds **5**, **6**, **17** and **19** were provided by Prof. A. Rustaiyan). Compound **18** was obtained by $NaBH_4$ reduction (MeOH, −15°, 1 hr) of **18a**, kindly provided by Dr A. H. Meriçli.

1-*Oxogermacra*-4,10(14)-*dien*-6β,7α,11αH-12,6-olide (**2**). Colourless oil, $[\alpha]_D^{23} + 83°$ ($CHCl_3$; *c* 0.2); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1789, 1682, 990 EIMS (probe) *m/z* (rel. int.): 248 $[M]^+$ (4), 233 $[M-Me]^+$ (2), 230 $[M-H_2O]^+$ (2), 220 $[M-CO]^+$ (3), 205 (2), 202 (2), 175 (14), 137 (32), 55 (100). High resolution MS: found, $M_r = 248.1423$;

Table 2. ^{1}H NMR data of eudesmanolides **9–12**, **16**, and **18***

H	9	10	11	12	16	18
1	3.50 *dd*	3.51 *dd*	3.52 *dd*	3.53 *dd*	4.63 *br d*	3.53 *dd*
2α	1.83 *dddd*	1.83 *dddd*	1.73 *br m*	1.75 *br m*	2.43 *br d*	1.72 *m*
2β	1.60 *br m*	1.55 *br m*			2.07 *br d*	
3α	2.10 *m*	2.12 *m*	2.15 *m*	2.17 *m*		
					5.29 *br s*	2.10 *m*
3β	2.30 *ddd*	2.33 *ddd*	2.02 *dddd*	2.01 *dddd*		
5	2.05 *br d*	2.08 *br d*	—	—	2.58 *br d*	—
6	4.05 *t*	4.27 *t*	4.58 *ddq*	4.80 *ddq*	3.95 *dd*	4.56 *ddq*
7	1.49 *m*	1.55 *br m*	1.73 *br m*	2.15 *dddd*		1.80 *ddd*
8α	1.89 *dddd*	1.73 *dddd*	1.95 *dddd*	1.75 *br m*	1.65 *br m*	—
8β	1.60 *br m*	1.55 *br m*	1.52 *dddd*	1.60 *dddd*		3.95 *ddd*
9α	1.28 *ddd*	1.31 *ddd*	1.29 *ddd*	1.29 *ddd*	1.85 *m*	1.27 *dd*
9β	2.05 *ddd*	2.05 *ddd*	2.07 *ddd*	2.06 *ddd*	1.36 *m*	2.32 *dd*
11	2.30 *dq*	2.65 *dq*	2.26 *dq*	2.64 *dq*	2.29 *dq*	2.52 *dq*
13	1.22 *d*	1.21 *d*	1.24 *d*	1.19 *d*	1.23 *d*	1.39 *d*
14	0.82 *s*	0.82 *s*	1.11 *s*	1.09 *s*	0.93 *s*	1.10 *s*
15	4.97 *br s*	4.98 *br d*	1.84 *br s*	1.83 *br s*	1.86 *br s*	1.85 *br s*
	4.82 *br s*	4.84 *br d*				
AcO	—	—	—	—	2.08 s	—

*At 400 MHz in $CDCl_3$ (27°).

Coupling constants in Hz: **9** and **10** $J_{1,2\alpha} = J_{2\alpha,3\alpha} = 4.5$; $J_{1,2\beta} = 11.5$; $J_{2\alpha,2\beta} = 12.5$; $J_{2\alpha,3\beta} = 2.5$; $J_{2\beta,3\beta} = 5$; $J_{3\alpha,3\beta} = 14$; $J_{5,6} = J_{6,7} = 11$; $J_{3\alpha,15} = J_{5,15} = 1.5$; $J_{7,8\alpha} = J_{8\alpha,9\alpha} = J_{8\alpha,9\beta} = 4$; $J_{8\alpha,8\beta} = 13$; $J_{8\beta,9\beta} = 3$; $J_{8\beta,9\alpha} = J_{9\alpha,9\beta} = 13.5$. **9** $J_{7,11} = 12$; $J_{11,13} = 7$. **10** $J_{7,11} = J_{11,13} = 7.5$. **11** and **12** $J_{1,2\alpha} = 4.5$; $J_{2\alpha,3\beta} = 2$; $J_{2\beta,3\beta} = 5.5$; $J_{3\alpha,3\beta} = 18$; $J_{3\beta,6} = 1.5$; $J_{7,8\beta} = J_{8\alpha,8\beta} = J_{8\beta,9\alpha} = 13$; $J_{7,8\alpha} = 3.5$; $J_{8\alpha,9\beta} = 2.5$; $J_{8\beta,9\beta} = J_{8\alpha,9\alpha} = 4$; $J_{9\alpha,9\beta} = 13.5$. **11** $J_{1,2\beta} = 10.5$; $J_{6,7} = 10.5$; $J_{7,11} = 12$; $J_{11,13} = 7$. **12** $J_{1,2\beta} = 11.5$; $J_{6,7} = 11.5$; $J_{7,11} = J_{11,13} = 7.5$. **16** $J_{1,2\beta} = 4.5$; $J_{2\alpha,2\beta} = 18$; $J_{5,6} = 11.5$; $J_{6,7} = 10$; $J_{7,11} = 12$; $J_{11,13} = 7$. **18** $J_{1,2\alpha} = 6$; $J_{1,2\beta} = 10$; $J_{6,7} = 11.6$; $J_{3\beta,6} = J_{6,15} = 1.5$; $J_{7,8} = J_{8,9\alpha} = 10.5$; $J_{8,9\beta} = 4.5$; $J_{7,11} = 11.7$; $J_{11,13} = 7$.

Table 3. ^{13}C NMR data of compounds **9–12** and **18**

C	9	10	11	12	18
1	78.23	78.32	77.69	77.67	77.45
2	31.25	31.26	27.06	27.08	26.78
3	33.53	33.57	33.28	33.34	33.28
4	142.81	142.90	125.98[a]	126.00[a]	126.93[a]
5	52.48[a]	52.98	128.85[a]	129.30[a]	127.34[a]
6	79.34	78.29	83.02	82.07	79.65
7	52.33[a]	48.08	52.81	48.24	58.61
8	23.01	20.33	24.43	21.18	70.04
9	35.98	35.97	38.26	38.22	48.66
10	42.85	42.66	41.90	41.72	41.01
11	41.18	38.70	41.13	38.05	40.82
12	179.38	180.02	179.03	179.77	178.73
13	12.48	9.68	12.41	9.81	14.35
14	11.64	11.65	18.47	18.45	19.62
15	110.28	110.41	19.77	19.72	19.62

*At 50.32 MHz in $CDCl_3$ (27°).

[a]The signals with this superscript may be interchanged within the corresponding spectrum.

calc. for $C_{15}H_{20}O_3$: M_r 248.1412. For ^{1}H NMR data, see Table 1.

1β,8α-*Dihydroxygermacra*-4,10(14)-*dien*-6β,7α,11αH-12,6-*olide* (11-*epishonachalin* A) (**7**). Colourless gum, $[\alpha]_D^{23} + 105°$ ($CHCl_3$; *c* 0.4);. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3480, 1785. EIMS (probe) *m/z* (rel. int.): 266 $[M]^+$, (1) 248 $[M-H_2O]^+$ (7), 220 $[M-H_2O-CO]^+$ (3), 193 (11), 175 (21), 93 (100). High resolution MS: found: M_r 248.1413; calcd for $C_{15}H_{20}O_3$, M_r 248.1412. For ^{1}H NMR data, see Table 1.

1β-*Hydroperoxy*-8α-*hydroxygermacra*-4,10(14)-*dien*-6β,7α,11βH-12,6-*olide* (**8**). Ustable, viscous gum, $[\alpha]_D^{23} + 50°$ ($CHCl_3$; *c* 0.2). EIMS (probe) *m/z* (rel. int.): 248 $[M-H_2O_2]^+$, (3), 69 (95), 55 (100). High resolution MS: found: M_r 248.1412; calc. for $C_{15}H_{20}O_3$, M_r 248.1412. For ^{1}H NMR data, see Table 1. Reaction of **8** with triphenylphosphine in CH_2Cl_2 at room temp. gave **6**.

1β-*Hydroxyeudesm*-4(15)-*en*-5α,6β,7α,11αH-12,6-*olide* (11α,13-*dihydroreynosin*) (**10**). Colourless needles, mp 148–149° (pentane–Et_2O), $[\alpha]_D^{23} + 155°$ ($CHCl_3$; *c* 0.3); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 1765, 1240, 1200, 940. EIMS (probe) *m/z* (rel. int.): 250 $[M]^+$ (12), 235 $[M-Me]^+$ (3), 232 $[M-H_2O]^+$ (100), 217 (10), 207 (11), 55 (95). High resolution MS: found M_r 250.1579; calc. for $C_{15}H_{22}O_3$, M_r 248.1569. For NMR data, see Tables 2 and 3.

1β-Hydroxyeudesm-4-en-6β,7α,11αH-12,6-olide (*11-epiartesin*) (**12**). Colourless needles, mp 126–127° (pentane–Et_2O), $[\alpha]_D^{23}$ +82° ($CHCl_3$; *c* 0.6); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 1775. EIMS (probe) *m/z* (rel. int.): 250 $[M]^+$ (22), 235 $[M-Me]^+$ (9), 232 $[M-H_2O]^+$ (16), 222 (7), 217 (14), 206 (68), 193 (38), 165 (52), 109 (58), 81 (100). High resolution MS: found: M_r 250.1575; calc. for $C_{15}H_{22}O_3$, M_r 250.1569. For NMR data, see Tables 2 and 3.

1α-Acetoxyeudesm-3-en-5α,6β,7α,11βH-12,6-olide (*11β,13-dihydrodouglanin acetate*) (**16**). Viscous gum, $[\alpha]_D^{23}$ +154° ($CHCl_3$; *c* 0.1). EIMS (probe) *m/z* (rel. int.): 232 $[M-HOAc]^+$ (100), 217 $[M-Me-HOAc]^+$ (33), 175 (28), 143 (57), 55 (97). High resolution MS: found, m_r 232.1463; calcd for $C_{15}H_{20}O_2$, M_r 232.1464. For ^1H NMR data, see Table 2.

1β,8α-Dihydroxyeudesm-4-en-6β,7α,11βH-12,6-olide (**18**). Small white needles, mp 92–94° (hexane–EtOAc); IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1746 (lactone), 1240, 1155, 970 EIMS (probe) *m/z* (rel. int.): 266 $[M]^+$ (28), 251 $[M-Me]^+$ (5), 248 $[M-H_2O]^+$ (21), 233 $[M-Me-H_2O]^+$ (7), 230 $[M-2H_2O]^+$ (14), 223 $[M-Me-CO]^+$ (20), 222 (100), 209 (29), 204 (29), 191 (25), 181 (36), 175 (39), 163 (43), 135 (53), 107 (50), 91 (55), 43 (42). High resolution MS: found: M_r 248.1420; calc. for $C_{15}H_{20}O_3$, M_r 248.1412. For NMR data, see Tables 2 and 3.

4,5-Dihydroxysantolina-1,8-diene (**20**). Colourless oil, $[\alpha]_D^{23}$ −8° ($CHCl_3$; *c* 0.9). ^1H NMR ($CDCl_3$): δ5.32 (*ddd*, *J* = 17, 10, 10 Hz), 5.04 (*dd*, 1H, *J* = 17, 1.5 Hz), 5.00 (*dd*, 1H, *J* = 10, 1.5 Hz), 4.86 (*br s*, 1H), 4.77 (*dq*, 1H, *J* = 1.5, 1.5 Hz), 4.31 (*d*, 1H, *J* = 10 Hz), 2.35 (*dd*, 1H, *J* = 10, 10 Hz), 1.70 (*br s*, 3H), 1.29 (*s*, 3H), 1.19 (*s*, 3H).

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REFERENCES

1. Vallés Xirau, J. (1986) Ph.D. Thesis, University of Barcelone, Spain.
2. Segal, R., Feuerstein, I. and Danin, A. (1987) *Biochem. Syst. Ecol.* **15**, 411.
3. Pathak, V. P. and Khanna, R. N. (1987) *Phytochemistry* **26**, 2103.
4. Gonzalez, A. G., Bermejo, J., Mansilla, H., Galindo, A., Amaro, J. M. and Massanet, G. M. (1978) *J. Chem. Soc. Perkin Trans I*, 1243.
5. Gordon, M. M., Van Derveer, D. and Zalkow, L. H. (1981) *J. Nat. Prod.* **44**, 432.
6. Rustaiyan, A., Zare, K., Ganji, T. M. and Sadri, H. A. (1989) *Phytochemistry* **28**, 1535.
7. Serkerov, S. V. and Aleskerova, A. N. (1985) *Khim. Prir. Soedin.*, 196.
8. Akyev, B., Kasymov, S. Z. and Sidyakin, G. P. (1972) *Khim. Prir. Soedin.*, 733.
9. Samek, Z., Holub, M., Bloszyk, E., Drozdz, B. and Herout, V. (1975) *Coll. Czech. Chem. Comm.* **40**, 2676.
10. Gonzalez, A. G., Bermejo, J., Mansilla, H., Massanet, G. M., Cabrera, I., Amaro, J. M. and Galindo, A. (1977) *Phytochemistry* **16**, 1836.
11. Serkerov, S. V. and Aleskerova, A. N. (1981) *Khim. Prir. Soedin.*, 564.
12. Fernández, I., Garcia, B. and Pedro, J. R. (1987) *Tetrahedron* **43**, 805.
13. Serkerov, S. V. and Aleskerova, A. N. (1983) *Khim. Prir. Soedin.*, 578.
14. Banerjee, S., Grenz, M., Jakupovic, J. and Bohlmann F. (1985) *Planta Med.* **51**, 177.
15. Bohlmann, F., Umemoto, K., Jakupovic, J., King, R. M. and Robinson, H. (1984) *Phytochemistry* **23**, 1669.
16. Sanz, J. F., Barberá, O. and Marco, J. A. (1989) *Phytochemistry* **28**, (in press).
17. Narayanan, C. R. and Venkatasubramanian, N. K. (1968) *J. Org. Chem.* **33**, 3156.
18. Van Hijfte, L. and Vandewalle, M. (1984) *Tetrahedron* **40**, 4371.
19. Moss, G. P., Pregosin, P. S. and Randall, E. W. (1974) *J. Chem. Soc. Perkin Trans. I*, 1525.
20. Delgado Gomis, J., Marco, J. A., Pedro Llinares, J. R., Sánchez Parareda, J., Sendra, J. M. and Seoane, E. (1979) *Phytochemistry* **18**, 1523.
21. González, A. G., Bretón, J. L. and Stockel, J. (1974) *An. Quim.* **70**, 231.
22. San Feliciano, A., Medarde, M., Poza, M. T. and Miguel Del Corral, J. M. (1986) *Phytochemistry* **25**, 1757.
23. Greger, H., Zdero, C. and Bohlmann, F. (1986) *Phytochemistry* **25**, 891.
24. Matsueda, S. and Geissman, T. A. (1967) *Tetrahedron Letters* 2159.
25. Meriçli, A. H., Jakupovic, J., Bohlmann, F., Damadyan, B., Ozhatay, N. and Çubukçu, B. (1988) *Planta Med.* **54**, 447.
26. Bohlmann, F., Zdero, C., King, R. M. and Robinson, H. (1984) *Phytochemistry* **23**, 1979.