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NEW GERMACRANOLIDES AND EUDESMANOLIDES FROM NORTH AFRICAN *ARTEMISIA HERBA-ALBA*

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ABSTRACT.—Specimens of *Artemisia herba-alba* collected in two North African locations afforded four new germacranolides, a new eudesmanolide, and a new C_{11}-acid related to davanone. Their structures were established through a combination of spectroscopic techniques and chemical correlations. Furthermore, a corrected structure is proposed for the elemanolide, shonachalin D.

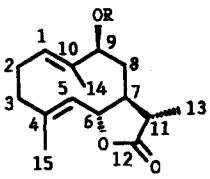
Artemisia herba-alba Asso (Asteraceae), a medicinal plant that occurs around the Mediterranean basin, has been the object of several previous chemical studies. Segal and co-workers investigated chemotypes of *A. herba-alba* collected in various locations in Egypt and Israel and isolated several new germacranolides and eudesmanolides, named herbolides A–J (1). Spanish subspecies of *A. herba-alba* were studied by our group. In the course of these studies, we obtained a number of sesquiterpene lactones with the germacrane and eudesmane framework, many of which are novel (2–6). A striking difference between our compounds and those isolated by Segal *et al.* was the presence of oxygen functions at C-9 (germacrane and eudesmane numbering) in lactones from the African specimens. Another group did not find lactones of this type in plant material collected in the Sinai desert (7). Nevertheless, a recent investigation on an Egyptian specimen afforded some new sesquiterpene lactones, with two of them bearing oxygen functions at C-9 (8). Intrigued by these differences in the chemical composition, which could perhaps reflect taxonomic differences at the subspecies or even species level, we investigated *A. herba-alba* collected in Morocco and Tunisia (9,10). The results of this study are described in this communication.

RESULTS AND DISCUSSION

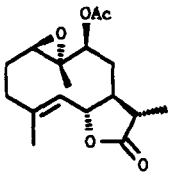
The plant material collected from both North African locations contained similar sesquiterpene lactones. In addition to herbolide A [**1**] (11), its deacetyl derivative [**2**] (11), herbolide B [**3**] (11), herbolide D [**5**] (12), the eudesmanolide [**10**] (8), balchanolide (13), 8α-acetoxytaurin (14), 11β,13-dihydroanhydroverlotorin (15), shonachalin A (15), spathulenol (16), the coumarin, herniarin, and *p*-hydroxyacetophenone, we isolated the new products **4** (deacetylherbolide D) **6**, **7**, **8**, and **9**. In addition, the material from Morocco furnished the davanone-like derivatives **11**–**16** (7,17), with compound **12** being novel.

Lactone **4**, $C_{15}H_{22}O_4$, displayed ir absorption bands at 3400 and 1760 cm^{-1}, which indicated the presence of hydroxyl and lactone functions. The nmr spectra (Tables 1 and 2) were very similar to those of **5** but no acetate signals were present. The main difference in the ^{1}H-nmr spectrum was the shift of H-9 from δ 4.75 in **5** (12) to δ 3.91 in **4**. The conclusion that **4** was the deacetyl derivative of **5** was confirmed by acetylation of both **4** and **5**, to give the same diacetyl derivative, **17** (Tables 3 and 4).

Lactone **6**, $C_{17}H_{24}O_6$, displayed ^{1}H-nmr data (Table 1) similar to those of **5** but the



1 R=Ac
2 R=H



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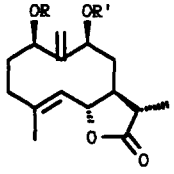
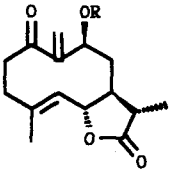
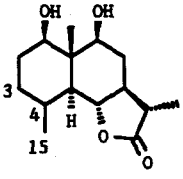


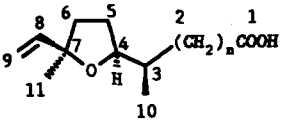
4 R=R'=H
5 R=H, R'=Ac
6 R=OH, R'=Ac
17 R=R'=Ac



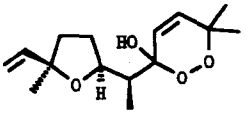
7 R=H
8 R=Ac



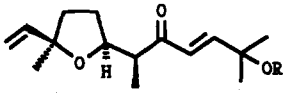
9 Δ^3
10 $\Delta^{4(15)}$



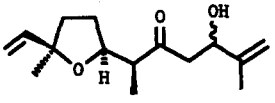
11 n=0
12 n=1



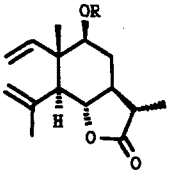
13



14 R=H
15 R=OH



16



21 R=Ac
22 R=H

$\xrightarrow{K_2CO_3/MeOH}$

signal of H-1 appeared at lower field (δ 4.17, br d). This and the broadened singlet at δ 8.75 suggested a hydroperoxide group at C-1. The structure was finally confirmed by photooxygenation of **1** to give **6** and by reduction of **6** with PPh_3 to give **5**.

The nmr spectra of keto lactones **7** and **8** (ir ν max 1770, 1670 cm^{-1}), measured at 57° due to signal broadening at room temperature (Tables 1 and 2), showed that the latter was the acetyl derivative of the former. Accordingly, acetylation of **7** gave **8**. The proposed structures, deduced from spin decoupling, were finally confirmed by dehydration of **6** with Ac_2O to yield **8**.

The sharp three-proton singlet at 1.00 ppm in the ^{1}H-nmr spectrum of **9** (Table 1) suggested that it was an eudesmanolide. The ^{1}H-nmr data were close to those of **10** (8) but the exocyclic methylene was replaced by a trisubstituted double bond (^{13}C nmr, Table 2). Spin-decoupling experiments supported the structure, which was finally confirmed by chemical synthesis. As depicted in Scheme 1, the stereoselective epoxidation of **1** and **2** at either one or both double bonds afforded monoepoxy and diepoxy lactones **3**, **18**, **19**, and **20** (for nmr spectra, see Tables 3 and 4 and Segal *et al.* [11]). Treatment of **20** (deacetylherbolide B) with catalytic amounts of camphorsulfonic acid at room temperature afforded a 5:1 mixture of eudesmanolides **9** and **10**, together with trace amounts of the corresponding Δ^4-isomer (Experimental). This definitively settled the structure of both compounds, as the stereostructure of **3** (herbolide B) has already been secured via X-ray analysis (18).

Compound **12**, $C_{11}H_{18}O_3$, was found to be an acid (ir broad band from 3500-2500 cm^{-1}, carbonyl band at 1700 cm^{-1}). Nmr data (Experimental) and spin-decoupling

TABLE 1. ^{1}H-Nmr Spectra of Compounds **4** and **6–9** (400 MHz, $CDCl_3$).[a]

Proton	Compound				
	4	**6**[b]	**7**[c]	**8**[c]	**9**
H-1	3.82 br d (9)	4.17 br d (10.5)	—	—	4.01 dd (10, 7)
H-2α		2.15 m[d]	2.75 ddd (12, 6.5, 3)	2.39 ddd (12, 6, 2.7)	2.38 ddddq (18, 7, 2, 2, 2)
H-2β	2.20–2.00 m[d]	1.90 m[d]	2.95 ddd (12, 12, 7)	3.20 ddd (12, 12, 6)	2.00 m[d]
H-3α	1.85–1.75 m[d]	2.25–2.15 m[d]	2.54 ddd (12, 12, 6.5)	2.52 ddd (12, 12, 6)	5.34 br m
H-3β		2.25–2.15 m[d]	2.39 ddd (12, 6.5, 3)	2.32 ddd (12, 6, 2.7)	
H-5	5.00 br d (10)	5.18 br d (10)	4.94 br d (10)	4.93 br d (10.5)	2.20 br d (11.5)
H-6	4.20 br dd (10, 9.5)	4.28 br dd (10, 9)	4.32 dd (10, 10)	4.28 dd (10.5, 9.5)	3.94 dd (11.5, 10)
H-7	1.85–1.75 m[d]	1.95 m[d]	1.60 m	1.84 br ddd (12, 10, 9.5)	1.63 m[d]
H-8α	2.10 m[d]	2.00–1.80 m[d]	2.10 br d (14)	2.15 m[d]	2.10 m[d]
H-8β	1.85–1.75 m[d]	2.00–1.80 m[d]	1.70 m[d]	1.63 ddd (14, 10, 10)	1.63 m[d]
H-9	3.91 br d (8.5)	5.09 br d (9)	4.36 br d (10.5)	5.67 br d (10)	3.90 dd (10, 5)
H-11	2.20 dq (12, 7)	2.25 m[d]	2.25 dq (12, 7)	2.15 dq (12, 7)	2.33 m[d]
H-13	1.20 d (7)	1.24 d (7)	1.26 d (7)	1.25 d (7)	1.22 d (7)
H-14	5.26 br s	5.47 br s	5.97 br s	6.00 br s	1.00 s
	5.23 br s	5.43 br s	5.90 br s	5.97 br s	
H-15	1.50 br s	1.56 br s	1.72 br s	1.72 br s	1.81 br s
OAc	—	2.02 s	—	2.00 s	—

[a]Data are δ (ppm), multiplicity and *J* (parentheses) in Hz.
[b]Signal of OOH: δ 8.75 br s.
[c]Measured at 57°.
[d]Complex overlapped multiplet.

TABLE 2. ^{13}C-Nmr Spectra of Compounds **4** and **6–10** (75 MHz, $CDCl_3$).[a]

Carbon	Compound					
	4	**6**	**7**[b]	**8**[b]	**9**	**10**
C-1	76.6	90.2	204.5	201.5	77.2	79.9
C-2	33.1	28.6	36.3	34.4	33.4	31.5
C-3	37.4	37.7	37.6	38.4	120.8	33.2
C-4	146.4	146.4	140.9	141.3	132.8	141.4
C-5	121.7	121.6	126.3	125.3	48.9	50.6
C-6	80.3	80.0	80.1	80.0	80.2	78.4
C-7	51.6	51.6	50.2	50.2	50.1	48.7
C-8	37.9	35.6	37.4[c]	37.6	30.9	31.0
C-9	76.7	77.9	72.7[c]	70.6	77.8	79.1
C-10	155.8	147.0	152.6[c]	151.3	43.6	45.7
C-11	41.7	41.6	42.1	41.9	40.4	40.9
C-12	178.5	178.0	177.6	177.2	179.2	179.0
C-13	12.7	12.7	12.8	12.7	12.4	12.4
C-14	111.2	117.2	124.7	124.8	6.6	7.0
C-15	17.9	17.6	16.8	17.0	23.2	111.6
OAc	—	170.8	—	169.3	—	—
		21.4		21.0		

[a]Data are δ (ppm). Signals have been assigned with 2D-COSY.
[b]Measured at 57°.
[c]Broadened signal.

TABLE 3. ^{1}H-Nmr Spectra of Compounds **17**, **19**, **21**, and **22** (400 MHz, $CDCl_3$).[a]

Proton	Compound			
	17	**19**	**21**[b]	**22**[b]
H-1	5.02 br d (10.5)	2.90 dd (11, 1.5)	5.63 dd (17.5, 10.7)	5.72 dd (17.5, 10.7)
H-2α	2.10 m[c]	2.20 dddd (14, 5.5, 2.5, 2.5)	5.08 br d (10.7)	5.29 br d (10.7)
H-2β	1.90 m[c]	1.59 dddd (14, 13, 11, 5)	4.96 br d (17.5)	5.12 br d (17.5)
H-3α	2.30 br ddd (13, 13, 4)	1.35 m[c]	4.70 br s	4.70 br s
H-3β	2.15 m[c]	2.25 ddd (13.5, 5, 2.5)	5.06 br s	5.02 t (1.5)
H-5	5.25 br d (10)	2.70 d (9)	2.32 br d (11.5)	2.29 br d (11.5)
H-6	4.25 br dd (10, 9.5)	3.90 dd (9, 9)	4.11 dd (11.5, 10.5)	4.13 dd (11.5, 11)
H-7	2.00 m[c]	2.00–1.85 m[c]	1.76 dddd (12, 12, 10.5, 3.5)	1.72 dddd (12, 12, 11, 3)
H-8α	1.95–1.80 m[c]	2.00–1.85 m[c]	2.10 ddd (12, 4.5, 3.5)	2.14 ddd (12.5, 4.3, 3)
H-8β	1.95–1.80 m[c]	2.00–1.85 m[c]	1.60 ddd (12, 12, 11.3)	1.55 ddd (12.5, 12, 11.2)
H-9	5.06 br d (9.5)	3.18 dd (10, 2.5)	4.87 dd (11.3, 4.5)	3.54 dd (11.2, 4.3)
H-11	2.20 dq (12, 7)	2.35 dq (12, 7)	2.39 dq (12, 7)	2.40 dq (12, 7)
H-13	1.24 d (7)	1.31 d (7)	1.23 d (7)	1.24 d (7)
H-14	5.49 br s 5.46 br s	1.36 s	1.13 s	1.05 s
H-15	1.58 br s	1.40 s	1.76 br s	1.77 br s
OAc	1.98 s (6H)	—	1.98 s	—

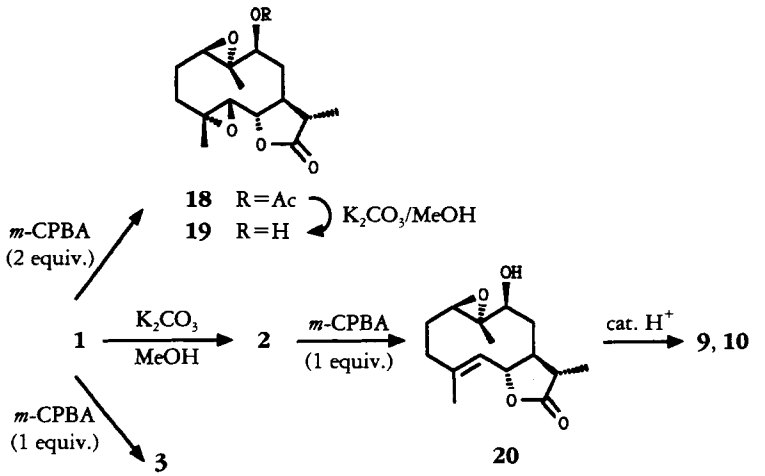
[a]Data are δ (ppm), multiplicity and *J* (parentheses) in Hz.
[b]In these compounds, H-2α...H-3β refer to the olefinic protons.
[c]Complex overlapped multiplet.

experiments indicated that it was structurally very close to **11** but with an additional CH_2 group. The proposed structure was firmly supported by long-range, 2D heteronuclear correlations (HMBC), which showed a correlation between the acid carbonyl carbon and

TABLE 4. ^{13}C-Nmr Spectra of Compounds **17–22** (75 MHz, $CDCl_3$).[a]

Carbon	Compound					
	17	**18**	**19**	**20**	**21**	**22**
C-1	76.6	61.3	63.5	67.2	144.0	145.1
C-2	30.9	22.8	23.3	23.4	114.8	116.2
C-3	37.0	35.2	35.1	36.0	116.1	115.6
C-4	146.1	60.1	60.5	143.5	139.5	140.0
C-5	122.0	64.4	64.0	124.1	54.6	54.3
C-6	80.0	81.2	80.6	79.8	79.8	80.1
C-7	51.5	47.4	48.3	51.3	48.5	48.8
C-8	35.3	32.8	33.8	33.8	28.5	29.7
C-9	77.2	81.5	79.4	78.9	75.6	74.5
C-10	147.6	60.9	63.7	64.7	47.2	48.9
C-11	41.6	42.9	42.3	42.2	41.5	41.4
C-12	178.0	176.5	176.4	177.8	178.5	178.7
C-13	12.7	13.0	13.0	13.0	12.5	12.5
C-14	116.8	12.4	11.5	11.8	11.9	10.7
C-15	18.1	17.0	17.0	17.9	24.3	24.0
OAc	170.0/169.9 21.2 (×2)	170.2 21.2	—	—	170.2 21.0	—

[a]Data are δ (ppm). Signals have been assigned with 2D-COSY.



SCHEME 1. Chemical Correlation of **1** with Eudesmanolides **9** and **10**.

a methylene group vicinal to a CH_3CH segment. The proposed absolute configuration has been tentatively assumed to be as in davanone.

From the biogenetic point-of-view, all these sesquiterpene lactones are obviously related. Their relationship might be similar to the one proposed for the corresponding 11,13-dehydro derivatives (19). In fact, the described chemical conversions are in vitro analogues of the suspected enzymatic processes.

The elemanolide shonachalin D, isolated several years ago from *A. fragrans,* was reported to have structure **22** (20). Cope rearrangement of **1** gave the elemanolide **21**, as expected, which on deacetylation (Experimental) yielded **22**. The physical and spectral data of both **22** and **21** were markedly different from those reported for shonachalin D (20) and the corresponding acetate. We believe that shonachalin D is most likely identical with either temisin or its 8-epimer (21). This proposal is based on the chemical shift of H-13 at δ 1.43 (20), a value expected when C-8 oxygen functions are present (22).

The results presented here indicate that oxygenation at C-9 may in fact be a distinct chemical feature of lactones isolated from North African *A. herba-alba.* This could perhaps suggest a taxonomic differentiation of the Spanish and African material as separate species, but more precise morphological studies will be necessary to support this proposal. Compounds **1** and **5** have also been recently found in *A. vallesiaca* (23).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotations were measured at 23°. Ir spectra were measured as films (oils) or KBr pellets (solids). ^{1}H- and ^{13}C-nmr spectra were measured at 400 and 75 MHz, respectively. Ms were measured on a Hewlett-Packard 5988A spectrometer in either the ei or the ci mode. Normal cc was carried out on Si gel (Merck 60–200 μm). Mplc was conducted on Si gel (Merck, 15–40 μm). Hplc was performed in Lichrosorb RP-8 columns (250×8 mm), flow rate 3 ml/min.

PLANT MATERIAL.—*A. herba-alba* was collected in July 1990, in the vicinity of Djebel Dokh, Morocco (aerial parts, dry wt, 1200 g), and in May 1992, in the vicinity of El-Karma, RN 14, km 109, Tunisia (aerial parts, dry wt, 1130 g). Voucher specimens have been registered as BCF-37105 and BCF-37203, respectively, in the Herbarium of the Laboratory of Botany, Faculty of Pharmacy, University of Barcelona, Spain.

EXTRACTION AND CHROMATOGRAPHY.—In each case, the plant material was processed according to a standard procedure (24). The defatted extract was prefractionated by cc on Si gel (A, hexane-Et_2O, 1:1; B, Et_2O and C, Et_2O-MeOH, 6:1). The three fractions were subjected to further chromatographic separation as described below.

Artemisia herba-alba from Morocco: Fraction A was fractionated by mplc on Si gel (hexane-Et_2O, 1:1). Where necessary, the intermediate fractions were further purified by prep. tlc or hplc to yield herniarin (15 mg), *p*-hydroxyacetophenone (30 mg), 8α-acetoxytaurin (11 mg), **1** (30 mg), **11** (157 mg), **12** (24 mg), **13** (263 mg), **14** (63 mg), **15** (67 mg), and **16** (31 mg). Fraction B was fractionated in the same way by mplc on Si gel (hexane-Et_2O, 1:3). The intermediate fractions were further purified by prep. tlc or hplc to yield mainly common flavonoids together with additional quantities of **14** (132 mg). Finally, mplc of fraction C (Et_2O-MeOH, 20:1), followed by prep. tlc or hplc allowed the isolation of **4** (144 mg), **5** (83 mg), **7** (10 mg), **9** (4 mg), and **10** (16 mg).

Artemisia herba-alba from Tunisia: Similar purification procedures were used. Fraction A yielded mainly spathulenol (41 mg) together with waxes and common sterols. Fraction B yielded herniarin (35 mg), *p*-hydroxyacetophenone (20 mg), **1** (507 mg), 11β,13-dihydroanhydroverlotorin (13 mg), and balchanolide (28 mg). Fraction C gave more **1** (65 mg), **2** (260 mg), **3** (70 mg), **4** (14 mg), **5** (430 mg), **6** (125 mg), **7** (30 mg), **8** (9 mg), **9** (5 mg), **10** (110 mg), and shonachalin A (30 mg).

1β,9β-Dihydroxygermacra-4,10(14)-dien-6β,11βH-12,6-olide (deacetylherbolide D) [**4**].—Oil, $[\alpha]^{22}D$ +37° (*c*=4.4, $CHCl_3$); ir ν max (film) 3400 (OH), 3055, 1760 (lactone C=O), 1445, 1260, 1175, 960, 905 cm^{-1}; eims *m/z* $[M]^+$ 266 (1), $[M-H_2O]^+$ 248 (1), $[M-2H_2O]^+$ 230 (2), 205 (6), 157 (5), 131 (9), 123 (10), 121 (13), 107 (20), 97 (10), 95 (27), 93 (30), 91 (42), 84 (38), 81 (27), 79 (39), 77 (36), 67 (33), 55 (100), 43 (82), 41 (93); nmr, see Tables 1 and 2.

1β-Hydroperoxy-9β-acetoxygermacra-4,10(14)-dien-6β,11βH-12,6-olide [**6**].—Oil, $[\alpha]^{22}D$ +16° (*c*=5.4, $CHCl_3$); ir ν max (film) 3400 (OH), 3055, 1768 (lactone C=O), 1731 (acetate C=O), 1458, 1377, 1250, 1192, 972, 919, 748 cm^{-1}; cims (CH_4) *m/z* $[M+H]^+$ 325 (6), $[M+H-H_2O]^+$ 307 (17), $[M+H-H_2O-C_2H_2O]^+$ 265 (10), 249 (20), 247 (30), 231 (42), 203 (14), 175 (9), 86 (18), 84 (27), 61 (100); nmr, see Tables 1 and 2.

1-Oxo-9β-hydroxygermacra-4,10(14)-dien-6β,11βH-12,6-olide [**7**].—Oil, $[\alpha]^{22}D$ +43° (*c*=1.2, $CHCl_3$); ir ν max (film) 3500 (OH), 3058, 1771 (lactone C=O), 1670 (ketone C=O), 1449, 1267, 1184, 971, 739 cm^{-1}; eims *m/z* $[M]^+$ 264 (1), $[M-Me]^+$ 249 (3), 235 (15), 191 (6), 163 (8), 135 (12), 123 (18), 121 (14), 107 (20), 93 (30), 91 (26), 85 (57), 83 (100), 55 (49); nmr, see Tables 1 and 2.

1-Oxo-9β-acetoxygermacra-4,10(14)-dien-6β,11βH-12,6-olide [**8**].—Oil, $[\alpha]^{22}D$ +27° (*c*=0.8, $CHCl_3$); ir ν max (film) 3057, 1773 (lactone C=O), 1737 (acetate C=O), 1677 (ketone C=O), 1457, 1370, 1264, 1237, 970, 736 cm^{-1}; eims *m/z* $[M-C_2H_2O]^+$ 264 (3), $[M-C_2H_2O-Me]^+$ 249 (3), 205 (28), 149 (56), 123 (88), 105 (50), 91 (69), 69 (75), 55 (87), 43 (100); nmr, see Tables 1 and 2.

1β,9β-Dihydroxyeudesm-3-en-5α,6β,11βH-12,6-olide [**9**].—Oil, $[\alpha]^{22}D$ +46° (*c*=0.35, $CHCl_3$); ir ν max (film) 3300 (OH), 3057, 1777 (lactone C=O), 1443, 1267, 1173, 1146, 1050, 992, 738 cm^{-1}; eims *m/z* $[M]^+$ 266 (10), $[M-H_2O]^+$ 248 (25), 233 (11), 205 (32), 175 (53), 149 (32), 123 (33), 121 (38), 119 (45), 107 (73), 91 (56), 69 (84), 55 (100), 43 (79); nmr, see Tables 1 and 2.

(3R,4S,7R)-3,7-Dimethyl-4,7-epoxynon-8-enoic acid [**12**].—Oil, $[\alpha]^{22}D$ −10° (*c*=3.5, $CHCl_3$); ir ν max (film) 3500-2500 (br, COOH), 1700 (acid C=O), 1440, 1410, 1370, 1265, 920, 735 cm^{-1}; eims *m/z* $[M-Me]^+$ 183 (14), $[M-H_2O]^+$ 180 (5), $[M-Me-H_2O]^+$ 165 (8), 137 (11), 135 (9), 119 (11), 111 (100), 109 (14), 95 (20), 93 (88), 91 (29), 84 (20), 81 (35), 67 (47), 55 (98), 43 (98), 41 (65); ^1H nmr (400 MHz, $CDCl_3$) δ 5.88 (1H, dd, *J*=17.3 and 10.7 Hz, H-8), 5.19 (1H, br d, *J*=17.3 Hz, H-9$_t$), 4.98 (1H, br d, *J*=10.7 Hz, H-9$_c$), 3.74 (1H, ddd, *J*=8.5, 8.5, and 6 Hz, H-4), 2.76 (1H, dd, *J*=15.5 and 5 Hz, H-2), 2.20 (1H, dd, *J*=15.5 and 8.5 Hz, H-2′), 2.00–1.60 (5H, br m, H-3, H-5, H-6), 1.29 (3H, s, H_3-11), 0.93 (3H, d, *J*=7 Hz, H_3-10); ^{13}C nmr (75 MHz, $CDCl_3$) δ 178.3 (C-1), 144.1 (C-8), 111.8 (C-9), 83.3 (C-4), 83.1 (C-7), 39.3 (C-2), 37.9 (C-6), 36.1 (C-3), 29.9 (C-5), 26.4 (C-11), 16.6 (C-10).

1β,9β-Diacetoxygermacra-4,10(14)-dien-6β,11βH-12,6-olide (herbolide D acetate) [**17**].—Oil, $[\alpha]^{22}D$ +131° (*c*=0.2, $CHCl_3$); ir ν max (film) 1775 (lactone C=O), 1736 (acetate C=O), 1443, 1369, 1242, 1184, 1022, 964 cm^{-1}; nmr, see Tables 3 and 4.

9β-Hydroxy-1β,10α;4α,5β-diepoxygermacran-6β,11βH-12,6-olide [**19**].—Colorless cubes, mp 222–223° (Et_2O), $[\alpha]^{22}D$ −35° (*c*=0.7, $CHCl_3$); ir ν max (KBr) 3450 (OH), 1752 (lactone C=O), 1442, 1165, 1044, 1018, 980, 795 cm^{-1}; nmr, see Tables 3 and 4.

9β-Acetoxyelema-1,3-dien-5α,6β,11βH-12,6-olide [**21**].—Oil, $[\alpha]^{22}D$ +1° (*c*=0.9, $CHCl_3$); ir ν max (film) 3085, 1758 (lactone C=O), 1720 (acetate C=O), 1438, 1361, 1232, 1007 cm^{-1}; eims *m/z* $[M]^+$ 292 (1), $[M-Me]^+$ 277 (1), $[M-C_2H_2O]^+$ 250 (2), $[M-HOAc]^+$ 232 (16), $[M-HOAc-Me]^+$ 217 (11), 177 (10), 176 (10), 159 (19), 121 (31), 107 (24), 93 (41), 55 (36), 43 (100); nmr, see Tables 3 and 4.

9β-Hydroxyelema-1,3-dien-5α,6β,11βH-12,6-olide [**22**].—Colorless cubes, mp 142–143° (hexane/Et_2O), $[\alpha]^{22}D$ +44° (*c*=0.7, $CHCl_3$); ir ν max (KBr) 3470 (OH), 3081, 1751 (lactone C=O), 1711 sh, 1630, 1438, 1224, 1004, 894, 752 cm^{-1}; eims *m/z* $[M]^+$ 250 (1), $[M-Me]^+$ 235 (3), $[M-H_2O]^+$ 232 (5),

$[M-H_2O-Me]^+$ 217 (7), 177 (11), 152 (22), 141 (28), 109 (54), 93 (76), 69 (66), 55 (100); nmr, see Tables 3 and 4.

ACETYLATIONS.—Standard procedure: Lactone **4** (26 mg, ca. 0.1 mmol) was dissolved in dry pyridine (0.5 ml) and treated with Ac_2O (0.5 ml). After standing for 12 h at room temperature, the reaction mixture was poured into brine (10 ml) and extracted with CH_2Cl_2 (2×10 ml). The organic layers were then washed successively with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine. After drying on anhydrous Na_2SO_4 and evaporation of the organic solvent *in vacuo*, the residue was chromatographed on Si gel (hexane-EtOAc, 1:1) to yield **17** (30 mg, 85%). Compounds **5** and **7** were acetylated in the same way to give **17** and **8**, respectively.

DEACETYLATIONS.—Standard procedure: Lactone **1** (44 mg, ca. 0.15 mmol) was treated with K_2CO_3 (42 mg, 0.30 mmol) in MeOH. After stirring at room temperature for 2.5 h, the reaction mixture was worked up as above and the residue was chromatographed on Si gel (hexane-EtOAc, 1:1) to yield **2** (34 mg, 92%). Compounds **18** and **21** were deacetylated under the same conditions to give **19** and **22**, respectively.

EPOXIDATIONS.—Standard precedure: Lactone **1** (38 mg, ca. 0.13 mmol) was dissolved in CH_2Cl_2 (5 ml) and treated with 85% *m*-chloroperbenzoic acid (29 mg, ca. 0.14 mmol). The reaction mixture was then stirred at room temperature for 2 h, diluted with CH_2Cl_2 (10 ml) and washed successively with 5% aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, and brine. After drying on anhydrous Na_2SO_4 and evaporation of the organic solvent *in vacuo*, the residue was chromatographed on Si gel (hexane-EtOAc, 3:2) to yield **3** (28 mg, 72%). Compound **2** was epoxidized in the same way to give **20**. The reaction of **1** with 3 equivalents of *m*-chloroperbenzoic acid (room temperature, 24 h), followed by work-up as above and cc on Si gel (hexane-EtOAc, 3:7) afforded **18** in 55% yield.

PHOTOOXYGENATION OF **1** TO **6**.—Lactone **1** (292 mg, 1 mmol) was dissolved in dry MeCN (50 ml) and photooxygenated for 2.5 h under the conditions described in ref. (25). The solvent was then evaporated *in vacuo* and the crude residue was chromatographed on Si gel (hexane-EtOAc, 1:1). Unchanged starting product (135 mg) was first eluted, followed by hydroperoxide **6** (69 mg, 40% based on consumed **1**).

DEOXYGENATION OF **6** TO **5**.—Hydroperoxide **6** (24 mg, 0.075 mmol) was dissolved in dry Me_2CO (3 ml) and treated with PPh_3 (21 mg, 0.08 mmol). After stirring at room temperature for 4 h, the reaction mixture was evaporated *in vacuo* and chromatographed on Si gel (hexane-EtOAc, 1:1). This furnished **5** (15 mg, 65%).

DEHYDRATION OF **6** TO **8**.—This reaction was performed as described above for the acetylations. Cc on Si gel (hexane-EtOAc, 1:1) afforded **8** in 38% yield.

ACID-CATALYZED CYCLIZATION OF **20** TO **9** AND **10**.—Epoxy lactone **20** (21 mg, ca. 0.08 mmol) was dissolved in CH_2Cl_2 (2 ml) and treated with camphorsulfonic acid (3 mg). The reaction mixture was then stirred at room temperature for 3 h, diluted with CH_2Cl_2 (7 ml), and poured into brine. The organic layer was washed again with 5% aqueous $NaHCO_3$ and brine, dried on anhydrous Na_2SO_4, and evaporated *in vacuo*. Cc of the residue on Si gel (hexane-EtOAc, 2:3) furnished **9** (15 mg, 71%), **10** (3 mg, 14%), and trace amounts of the Δ^4-isomer.

COPE REARRANGEMENT OF **1** TO **21**.—Lactone **1** (66 mg) was placed in a small, round-bottomed flask, which was then evacuated with an oil pump and heated at 240° for 10 min. After cooling to room temperature, the crude product was then directly chromatographed on Si gel (hexane-EtOAc, 7:3) to yield unchanged **1** (38 mg) and **21** (22 mg, 78% based on consumed **1**).

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