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7-EPI-EUDESMANES, EUDESMANOIC ACIDS, EUDESMANOLIDES AND OTHER SESQUITERPENES FROM *PLUCHEA DIOSCORIDIS*

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Key Word Index—*Pluchea dioscoridis*; Asteraceae; isolation; sesquiterpenes; 7-epi-eudesmanes; eudesmanoic acids; eudesmanolide; guaiane and xanthane epoxide derivatives.

Abstract—Re-examination of the chemical constituents of leaves of *Pluchea dioscoridis* afforded, in addition to known compounds, seven new sesquiterpene derivatives (two 7-epi-eudesmanes, two eudesmanoic acids, a eudesmanolide, a guaiane and a xanthane epoxide). The structures were elucidated by spectroscopic methods. © 1997 Elsevier Science Ltd. All rights reserved

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INTRODUCTION

The genus *Pluchea* (Asteraceae, Tribe Plucheae) with about 80 species distributed mainly in Asia, North and South America, Africa and Australia is composed of shrubs or herbs with or without resin canals [1]. So far, 15 species have been studied [2]. Characteristic constituents of the genus are eudesmane derivatives such as the pluchenines [3–11]. Previous investigation of *Pluchea dioscoridis* (L.) DC. [= *Conyza dioscoridis* (L.) Desf.] led to the isolation of acetylenes, eudesmanolides, eudesmanolide glycoside, eudesmanoic acids and sulphated flavonoid derivatives [12–17]. Reinvestigation of the chemical constituents of the leaves of *P. dioscoridis*, a common weed in Egypt [18], afforded in addition to several known compounds seven new sesquiterpene derivatives. The isolation and structure elucidation of these compounds are discussed in this paper.

RESULTS AND DISCUSSION

The dichloromethane–methanol extract of the leaves of *P. dioscoridis* gave, in addition to the 7-epi-eudesmanes **3** and **4** [19], costic and isocostic acids (**5**–**8**) [15, 20, 21], eudesmanolides (**11**, **12**) [13–15] and guaiane derivatives (**14**, **15**) [22, 23], seven new sesquiterpene derivatives including the 7-epi-eudesmanes **1** and **2**, the eudesmane acids **9** and **10**, the eudesmanolide **13**, the guaiane **16** and the xanthane epoxide **17**. The structures of the known compounds were elucidated by comparison of their ^{1}H and ^{13}C NMR spectral data with those in the literature.

The EI mass spectrum of compound **1** showed a $[M]^+$ at m/z 238 consistent with the molecular formula $C_{15}H_{26}O_2$. The fragmentation pattern exhibited two ion peaks at m/z 220 $[M-18]^+$ and 202 $[M-36]^+$, corresponding to the loss of one and two water molecules, respectively. This suggested that the oxygen-containing functionalities were hydroxyl groups. The ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) showed that an eudesm-3-ene with a 1,6-diol was present. In the ^{1}H NMR spectrum, two tertiary methyl signals at δ 0.89 and 1.86 were assigned to H-14 and H-15, respectively, while the isopropyl methyl signals H-12 and H-13 appeared at δ 1.03 and 0.96 (each *d*, $J = 6.5$ Hz). A downfield signal at δ 5.31 was assigned to H-3 and showed allylic coupling to the olefinic methyl signal H-15 at δ 1.86 in the ^{1}H-^{1}H COSY spectrum. This H-3 correlated with an olefinic methine carbon

Table 1. ^{1}H NMR spectral data of compounds **1** and **2** (400 M Hz, $CDCl_3$)

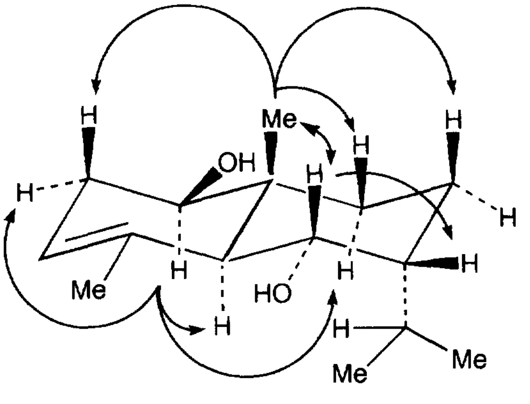
H	**1**	**2**
1	3.56 *dd*	3.47 *dd*
2α	2.25 *br d*	2.26 *br dd*
2β	1.92 *br d*	1.96 *br dd*
3	5.31 *br s*	5.41 *br s*
5	2.03 *br d*	1.85 *br s*
6	4.00 *dd*	4.26 *br s*
7	1.57 *m*	0.92 *m*
11	1.72 *m*	1.60 *m*
12	1.03 *d*	0.98 *d*
13	0.96 *d*	0.97 *d*
14	0.89 *s*	0.99 *s*
15	1.86 *br s*	1.80 *br s*

J (Hz): compound **1**: 1, 2α = 6; 1, 2β = 10; 2α, 2β = 17; 5, 6 = 9.5; 6, 7 = 5; 11, 12 = 11, 13 = 6.5.
compound **2**: 1, 2α = 6; 1, 2β = 10; 2α, 2β = 17; 11, 12 = 11, 13 = 7.

Table 2. ^{13}C NMR spectral data of compounds **1** and **2** (100 M Hz, CDCl$_3$, δ-values)

C	1*	2*	Multiplicity†
1	77.4	76.6	*d*
2	32.2	32.3	*t*
3	120.9	121.9	*t*
4	135.1	133.7	*s*
5	50.3	50.8	*d*
6	69.5	68.4	*d*
7	45.1	49.0	*t*
8	19.6	20.5	*t*
9	33.5	35.3	*t*
10	36.3	37.0	*s*
11	27.3	29.1	*d*
12	22.2	20.7	*q*
13	22.0	21.0	*q*
14	15.4	11.8	*q*
15	21.4	20.3	*q*

* Assignments were confirmed by ^{1}H-^{13}C COSY.
† Multiplicities deduced from DEPT experiments.



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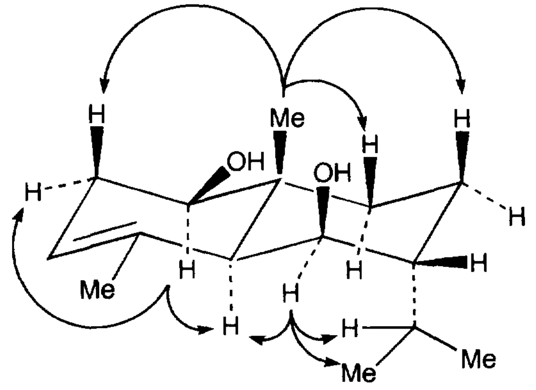

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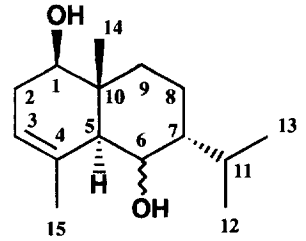
Fig. 1. NOEs observed in compounds **1** and **2**

signal at δ 120.9 in the 2D ^{1}H-^{13}C COSY spectrum and confirmed the presence of a Δ^3-double bond. The presence of a secondary hydroxyl group at C-1 followed from a proton signal at δ 3.56 (*dd*, $J = 10$, 6 Hz) which showed couplings in the ^{1}H-^{1}H COSY spectrum with H-2α at δ 2.25 and H-2β at δ 1.92. These couplings indicated the presence of a 1β-OH [19, 24]. On the other hand, a proton signal at δ 4.00 (*dd*, $J = 9.5$, 5 Hz) showed couplings with H-5 at δ 2.03 and H-7 at δ 1.57. This confirmed the presence of the second hydroxyl group at C-6. The relative configuration and stereochemistry at C-5, C-6 and C-7 were derived from the coupling constants ($J_{5,6} = 9.5$ and $J_{6,7} = 5$ Hz) which were in agreement with an (axial-axial and axial equatorial) pattern for these protons [14, 25]. This 5α,6α,7β(H) configuration was also proved from the clear NOEs (Fig. 1) between the angular methyl H-14, H-6 and between H-7, H-6 as well as between H-1α and H-5. The ^{13}C NMR spectral date (Table 2) also supported the structure. The multiplicities of the carbon signals were deduced from the DEPT experiments whereas the assignment of all proton signals and their connectivity to adjacent protons and carbon signals were established from the result of a 2D ^{1}H-^{1}H COSY experiment, together with the result of 2D ^{1}H-^{13}C COSY experiment. Thus **1** was identified as 1β,6α-dihydroxy-7-epi-eudesm-3-ene.

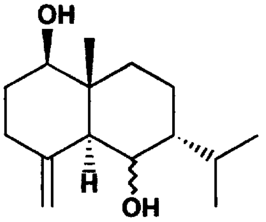
The molecular formula, $C_{15}H_{26}O_2$, for **2** was the same as that of **1** and the fragmentation pattern was similar, which indicated an isomer of **1**. The ^{1}H NMR spectrum (Table 1) was also very close to that of **1**. However, the hydrogen geminal to the hydroxyl group at C-6 appeared more downfield at δ 4.26 as a broad singlet. Thus H-6 was now axial and α-oriented [19]. In this configuration the dihedral angle between H-5/H-6 and between H-6/H-7 should be *ca* 90°. This was supported by clear NOEs (Fig. 1) between H-6, H-5, H-11 and H-12 and the absence of NOE between H-6 and the angular methyl H-14. The ^{13}C NMR spectrum (Table 2) also supported structure **2**, all signals being assigned by 2D ^{1}H and ^{1}H-^{13}C COSY experiments. Therefore, **2** is the C-6 epimer of **1**.

The EI-mass spectra, ^{1}H and ^{13}C NMR spectral data of compounds **3** and **4** were identical with those of the 7-epi-eudesmenes recently isolated from *Teucrium polium* [19]. Compounds **1**–**4** are the first eudesmanes with a 7-epi-configuration to be isolated from *Pluchea*.

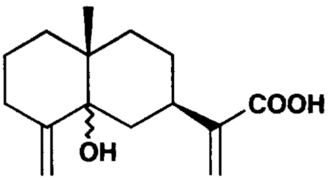
The ^{1}H NMR spectra of **9** and **10** (Table 3) were very similar to that of isocostic acid (**8**) isolated previously from the same species [15]. Major differences were observed in the signals of H-6 and H-15. A downfield singlet assigned to H-15 appeared at δ 9.50 in **9** and δ 9.54 in **10** instead of δ 10.17 in **8**. Also, H-6α was shifted upfield to δ 1.60 in **9**, and δ 1.57 in **10** compared with δ 3.55 in **8**. On the other hand, the ^{13}C NMR spectrum (Table 4) showed that the sp^2 signals of C-4 and C-5 in **8** were replaced by two signals of tertiary oxygenated carbons at δ 68.1 and 72.3 in **9** and δ 68.5 and 71.3 in **10**. The relative configuration and stereochemistry were derived from the coupling constants as well as NOE effects. The observed couplings between H-6α, H-6β and H-7 were the same as



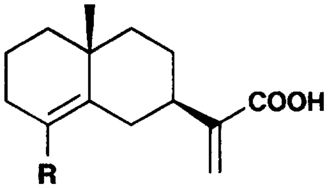
1 : 6α-OH
2 : 6β-OH



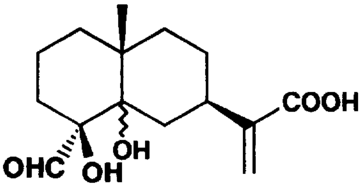
3 : 6α-OH
4 : 6β-OH



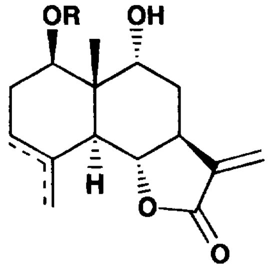
5 : 5α-OH
6 : 5β-OH



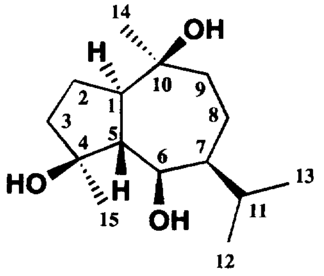
7 : R= CH_2OH
8 : R= CHO



9 : 5α-OH
10 : 5β-OH



11 : Δ^3, R= H
12 : Δ^3, R= Ang
13 : $\Delta^{4,15}$, R= H



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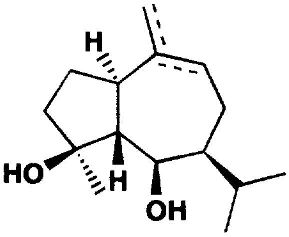
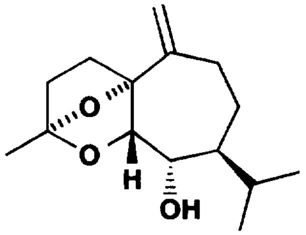


15 : $\Delta^{10,14}$
16 : Δ^9



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those in **8** indicating the same stereochemistry at C-7. The assumption that the 4-OH was β was substantiated by a clear NOE between H-15 and H-6α, while H-14 exhibited a NOE with H-6β. The configuration at C-5 could be deduced from the chemical shift of H-7 which appeared at δ 3.00 in **9** compared with δ 2.43 in **10**. Thus, **9** and **10** were epimers at C-5. The ^{13}C NMR spectra (Table 4) also supported the structures.

The molecular formula, $C_{15}H_{20}O_4$, for **13** (by HRMS) indicated that we were dealing with an isomer of the major constituent, the eudesmanolide **11** [14]. The ^{1}H NMR spectrum (Table 3) showed that a $\Delta^{4,15}$-double bond isomer was present. The stereochemistry was established from the coupling constants which were identical with those of **11**.

The ^{1}H NMR spectrum of **16** (Table 3) was very similar to that of the previously isolated teucladiol (**15**) [21, 22]. However, the exocyclic methylene signals were replaced by a broad doublet at δ 5.50 and a new olefinic methyl signal was observed at δ 1.66. Accordingly, compound **16** was the Δ^9-isomer of **15**. This was supported by the ^{13}C NMR spectrum (Table 4), which showed a trisubstituted double bond signals at δ 126.2 (*d*) and 139.2 (*s*) instead of the exomethylene signals. All proton signals could be assigned from the result of a 2D ^{1}H-^{1}H COSY experiment. The coupling constants showed that **16** has the same stereochemistry as **14** and **15** which was supported by the NOEs observed between H-6, H-7 and H-15 as well as between H-15, H-1 and H-6.

The high-resolution EI mass spectrum of com-

Table 3. ^1H NMR spectral data of compounds **9**, **10**, **13**, **16**, and **17** (400 M Hz, $CDCl_3$, δ-values)

H	**9**	**10**	**13**	**16**	**17**
1	*	*	4.12 *dd*	2.30 *m*	—
5	—	—	2.59 *d*	2.09 *dd*	4.05 *d*
6α	1.60 *dd*	1.57 *dd*	—	4.14 *dd*	—
6β	2.08 *t*	2.07 *t*	4.04 *t*	—	3.80 *t*
7	3.00 *ddd*	2.43 *br t*	3.16 *m*	1.27 *m*	2.17 *m*
9	*	*	4.08 *t*	5.50 *br d*	*
11	—	—	—	1.63 *m*	1.73 *m*
12	—	—	—	1.02 *d*	0.94 *d*
13	6.33 *br s*	6.33 *br s*	6.08 *d*	0.96 *d*	0.75 *d*
13′	5.66 *br s*	5.64 *br s*	5.38 *d*	—	—
14	1.12 *s*	1.15 *s*	0.80 *s*	1.66 *br s*	4.87, 4.92 *br s*
15	9.50 *s*	9.54 *s*	5.01, 4.91 *br s*	1.32 *s*	1.40 *s*

* Overlapping.

J[Hz]: Compound **9**: 6α, 6β = 6β, 7 = 7, 8β = 13; 6α, 7 = 7, 8 = 4 Hz; compound **10**: 6α, 6β = 6β, 7 = 8β, 7, 8β = 13; 6α, 7 = 3; compound **13**: 1, 2β = 12; 1,2α = 4; 5, 6 = 6, 7 = 11; 7, 13 = 7, 13′ = 3.5; 8α, 9 = 8β, 9 = 3.5; compound **16**: 1, 5 = 12; 5, 6 = 10; 8′, 9 = 9; 11, 12 = 11, 13 = 6.5; compound **17**: 5, 6 = 8; 6, 7 = 9; 11, 12 = 11, 13 = 7.

Table 4. ^{13}C NMR spectral data of compounds **7–10**, **16** and **17** (400 M Hz, $CDCl_3$, δ-values)

C	**7**	**8**	**9**	**10**	**16**	**17**
1	40.0 *t*	39.3 *t*	33.5 *t*	32.0 *t*	42.4 *d*	82.5 *s*
2	19.0 *t*	17.7 *t*	14.7 *t*	15.5 *t*	26.6 *t*	33.2 *t*
3	27.2 *t*	23.7 *t*	31.9 *t*	34.4 *t*	39.9 *t*	36.9 *t*
4	129.0 *s*	133.0 *s*	68.1 *s*	68.5 *s*	81.1 *s*	108.1 *s*
5	140.5 *s*	163.6 *s*	72.3 *s*	71.3 *s*	57.5 *d*	77.5 *d*
6	32.0 *t*	29.9 *t*	26.8 *t*	26.9 *t*	72.4 *d*	71.7 *d*
7	41.2 *d*	40.9 *d*	37.6 *d*	38.3 *d*	50.5 *d*	47.5 *d*
8	29.9 *t*	26.9 *t*	19.9 *t*	22.1 *t*	24.3 *t*	24.5 *t*
9	41.7 *t*	41.2 *t*	37.4 *t*	34.6 *t*	126.2 *d*	35.0 *t*
10	35.0 *s*	36.6 *s*	33.6 *s*	34.1 *s*	139.2 *s*	147.2 *s*
11	144.8 *s*	143.6 *s*	143.5 *s*	143.3 *s*	28.5 *d*	30.9 *d*
12	171.3 *s*	171.6 *s*	171.3 *s*	170.5 *t*	21.3 *q*	21.6 *q*
13	124.2 *t*	125.6 *t*	126.0 *t*	125.4 *t*	21.4 *q*	21.8 *q*
14	24.8 *q*	25.1 *q*	20.7 *q*	23.1 *q*	24.2 *q*	109.6 *t*
15	62.9 *t*	191.7 *s*	201.9 *s*	201.4 *s*	23.1 *q*	14.9 *q*

Multiplicities were deduced from DEPT experiments.

pound **17** showed a $[M]^+$ peak at *m/z* 252.3418 in agreement with the molecular formula $C_{15}H_{22}O_3$. The fragmentation pattern showed two peaks at *m/z* 236 $[M-16]^+$ and 234 $[M-18]^+$ corresponding to the loss of an oxygen atom and water molecule, respectively. The ^1H NMR spectrum (Table 3) was in part similar to that of **15**. However, the signal assigned to H-5 appeared as a doublet at δ 4.05, $J = 8$ Hz and was only coupled to H-6 at δ 3.80 indicating the absence of a proton at C-1. The chemical shift of the H-15 singlet at δ 1.40 required a position on an oxygen bearing carbon. Comparison of the ^{13}C NMR spectrum of **17** (Table 4) with that of **15** showed that the signals of C-1 and C-5 in **15** were replaced by signals of two oxygenated carbons [δ 82.5 (*s*) and δ 77.5 (*d*)], respectively. Furthermore, the signal of C-4 appeared at δ 108.1 compared with that at δ 80.8 in **15**. All these data clearly indicated the presence of two oxygen bridges between C-1 and C-4 and between C-4 and C-5. The stereochemistry and relative configuration of **17** were derived from the coupling constants as well as NOEs after inspection of the molecular model. The coupling constants $J_{5,6} = 8$ Hz and $J_{6,7} = 9$ Hz required a configuration 5β,6β,7α(H). This was supported by the NOEs observed between H-6, H-5, H-11 and H-12. Furthermore, the NOEs between H-5, H-2β and H-6 as well as between H-15 and H-3β showed that a 1α,4α-epoxide was present. Thus **17** was identified as 6α-hydroxy-1α,4α,4,5-diepoxyxanth-10(14)-ene.

EXPERIMENTAL

Plant material. Pluchea dioscoridis was collected in Egypt near El-Minia University campus, in April 1995. A voucher specimen is deposited in the Department of Botany, El-Minia University, Egypt.

Extraction and isolation. The air-dried leaves of *P.*

dioscoridis (2.5 kg) were extracted with CH_2Cl_2–MeOH (1:1) at room temp. and the solvent evapd *in vacuo*. The extract (65 g) was prefractionated as reported [26] into 4 frs by CC on silica gel eluting with petrol followed by a gradient of petrol–Et_2O up to 100% Et_2O. The frs (petrol–Et_2O, 1:1 and petrol–Et_2O, 1:4) were further sepd and purified by CC on silica gel, CC on Sephadex LH-20, prep. TLC as well as HPLC (MeOH–H_2O, 3:1 and 3:2, RP 8, $R_t = 2.4$ min, 8 i.d. and refractive index) to obtain pure **1** (13.6 mg), **2** (16.4 mg), **3** (6 mg), **4** (8 mg), **5** (9 mg), **6** (4 mg), **7** (1.4 g), **8** (0.8 g), **9** (5.4 mg), **10** (11.3 mg), **11** (0.8 g), **12** (30 mg), **13** (3.9 mg), **14** (5 mg), **15** (7 mg), **16** (6 mg) and **17** (5.2 mg).

1β,6α-Dihydroxy-7-epi-eudesm-3-ene (**1**). Oil, IR ν_{max}, $CHCl_3$, cm^{-1}; 3500, 3350 (OH); EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 238 $[M]^+$ ($C_{15}H_{26}O_2$) (15), 220 $[M-H_2O]^+$ (50), 202 $[M-2H_2O]^+$ (22), 205 $[220-Me]^+$ (17), 177 (50), 159 (45), 121 (60), 107 (100), 97 (47), 81 (40), 69 (25), 43 (35); $[\alpha]_D^{25}$ +44° ($CHCl_3$), *c* 0.52).

1β,6β-Dihydroxy-7-epi-eudesm-3-ene (**2**). Powder, IR ν_{max}, $CHCl_3$, cm^{-1}; 3460, 3350 (OH); EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 238 $[M]^+$ ($C_{15}H_{26}O_2$) (12), 220 $[M-H_2O]^-$ (55), 202 $[M-2H_2O]^+$ (60), 205 $[220-Me]^-$ (20), 177 (32), 159 (60), 121 (60), 107 (100), 97 (50), 81 (53), 55 (45), 43 (55).

4β,5α-Dihydroxy-15-oxo-eudesm-11(13)-en-12-oic acid (**9**). Gum, IR ν_{max}, $CHCl_3$, cm^{-1}; 3580 (OH), 1713 (COOH), 1705 (CHO); EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 282 $[M]^+$ ($C_{15}H_{22}O_5$) (3), 264 $[M-H_2O]^+$ (12), 246 $[M-2H_2O]^+$ (22), 217 $[246-CHO]^+$ (72), 192 (55), 145 (65), 120 (63), 111 (77), 91 (93), 55 (68), 55 (45), 43 (44), 41 (100); $[\alpha]_D^{26}$ +22.5° ($CHCl_3$, *c* 1.136).

4β,5β-Dihydroxy-15-oxo-eudesm-11(13)-en-12-oic acid (**10**). Gum, IR ν_{max}, $CHCl_3$, cm^{-1}; 3550 (OH), 1715 (COOH), 1708 (CHO); EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 282 $[M]^+$ ($C_{15}H_{22}O_5$) (1), 264 $[M-H_2O]^+$ (10), 246 $[M-2H_2O]^+$ (22), 217 $[246-CHO]^+$ (75), 182 (73), 145 (65), 120 (63), 111 (75), 91 (100), 79 (69), 55 (68), 55 (70), 43 (55), 41 (100); $[\alpha]_D^{26}$ −2.5° ($CHCl_3$, *c* 0.54).

1β,9α-Dihydroxyeudesm-4(15),11(13)-dien-5α,7αH-12,6α-olide (**13**). Oil, IR ν_{max}, $CHCl_3$, cm^{-1}; 3600 (OH), 1765 (γ-lactone); HR-EIMS: 264.3172 (calc. for $C_{15}H_{20}O_4$, 264.3190); EIMS (direct inlet) 70 eV, *m/z* (rel.int.): 264 $[M]^-$ (22), 246 $[M-H_2O]^+$ (100), 228 $[M-2H_2O]^+$ (71), 202 (93), 175 (45), 157 (58), 107 (60), 91 (83), 79 (53), 55 (52), 53 (58), 43 (46), 41 (52); $[\alpha]_D^{25}$ +17.5° ($CHCl_3$, *c* 0.39).

4β,6β-Dihydroxy-1α,5β(H)-guai-9-ene (**16**). Oil, IR ν_{max}, $CHCl_3$, cm^{-1}; 3420 (OH); EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 238 $[M]^+$ ($C_{15}H_{26}O_2$) (5), 220 $[M-H_2O]^+$ (45), 202 $[M-2H_2O]^+$ (25), 177 (27), 162 (100), 159 (95), 119 (88), 107 (40), 93 (47), 79 (35), 55 (28), 43 (59), 41 (38); $[\alpha]_D^{25}$ +10.5 ($CHCl_3$, *c* 0.60).

6α-Hydroxy-1,4,1α,5α-diepoxyxanth-10(14)-ene (**17**). Gum, IR ν_{max}, $CHCl_3$, cm^{-1}; 3450 (OH); HR-EIMS: 252.3418 (calc. for $C_{15}H_{24}O_3$, 252.3516); EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 252 $[M]^+$ (14), 236 $[M-O]^+$ (7), 234 $[M-H_2O]^+$ (12), 209 $[M-43]^+$ (15), 193 (81), 191 (40), 166 (78), 135 (54), 123 (40), 99 (80), 71 (35), 55 (33), 43 (100), 41 (52); $[\alpha]_D^{25}$ +22.6° ($CHCl_3$, *c* 0.52).

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