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A SESQUITERPENE LACTONE FROM *ARTEMISIA DIFFUSA*

A Rustaiyan, H Sigari, J. Jakupovic* and M. Grenz*

Department of Chemistry, Faculty of Science, Shahid Beheshty University, Eveen, Tehran, Iran, *Institute for Organic Chemistry, Technical University of Berlin, D-1000 Berlin 12, F R G

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Key Word Index—*Artemisia diffusa*, Compositae, sesquiterpene lactones, eudesmanolides, carbon skeleton

Abstract—The extract of the aerial parts of *Artemisia diffusa* afforded, in addition to several known eudesmanolides, two new eudesmanolides and a new type of sesquiterpene lactone with an eight-membered ring The structures were elucidated by high field NMR techniques and some chemical transformations.

INTRODUCTION

The large genus *Artemisia* (tribe Anthemideae) is rich in sesquiterpene lactones [1] In particular, 11,13-dihydroeudesmanolides are widespread However, other constituents are common [2]. In part, the chemistry seems to be useful for a separation of this genus into sections, but the results are still insufficient to give a clear picture. We now have studied a species from Iran, *Artemisia diffusa* Krasch ex P. Poljakov The results are discussed in this paper.

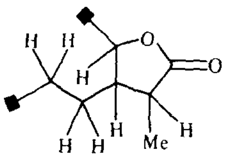
RESULTS AND DISCUSSION

The extract of the aerial parts gave phloracetophenone-2-*O*-4-*O*-dimethylether, cycloartenone, pinocarveol and the eudesmanolides **1b** [3], **2a** [4], **2b** [5], **3a** [6], **4** [7] as well as **1a** and **3a** Furthermore the lactone **8** and filifolide A (**11**) [8] were isolated

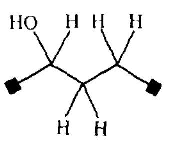
The structure of **1a** followed from its ^{1}H NMR spectrum (Table 1) which was similar to that of artemin (**1b**). However, the H-1 signal was a narrowly split triplet, indicating the axial orientation of the hydroxy group. The presence of a 5-hydroxy group followed indirectly from the H-6 signal which was only a doublet and from the missing coupling of H-15 with H-5 which is always visible in eudesmanolides with a proton at C-5.

The ^{1}H NMR spectral data of **3b** (Table 1) was similar to those of dehydro-*iso*-erivanin [9]. However, the H-1 signal indicated that lactone **3b** has an equatorial hydroxy group. Perhaps lactone **3b** is identical with alchanin [10] for which no complete stereochemistry has been given and insufficient NMR data are presented for a direct comparison to be made.

The unusual structure of compound **8** caused some problems as from the mass spectrum no clear molecular formula could be deduced. The highest peak m/z 280 was due to $C_{15}H_{20}O_5$ and the ^{13}C NMR spectrum (Table 2) showed four signals for oxygen-bearing carbons, one of them being at very low field (δ105 6) This required the presence of an acetal carbon The ^{1}H NMR spectrum (Table 3) indicated a secondary hydroxy group (δ3.40 *dd*) and a γ-lactone moiety (δ4 11 *d*, 2.31 *dq* and 1.21 *d*) and no further lowfield signals for protons at oxygen-bearing carbons. Spin decoupling led to the sequences A and B.



A



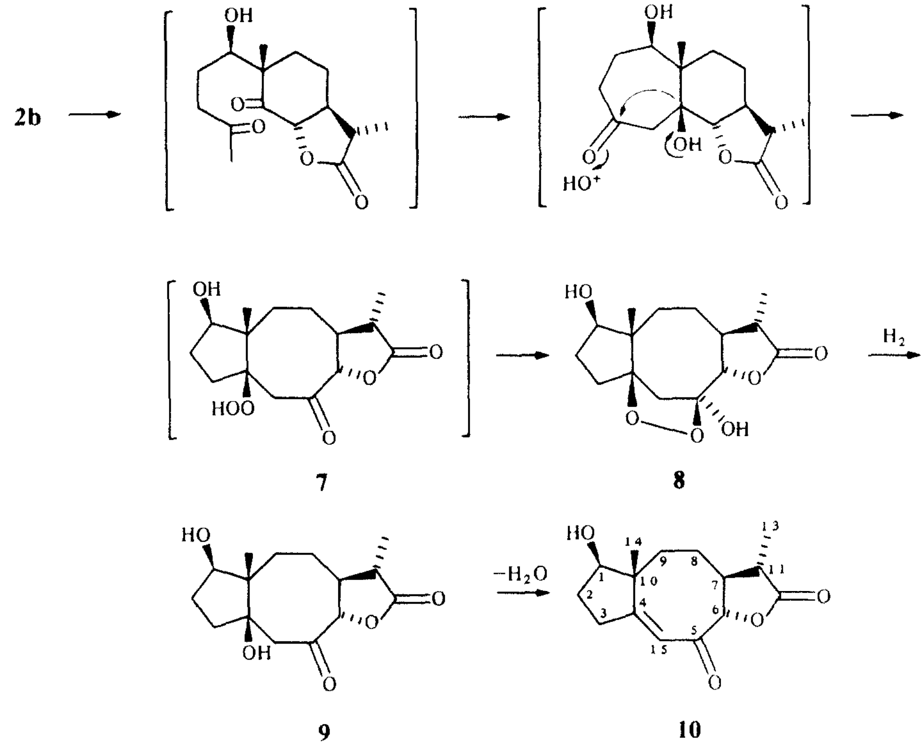
B

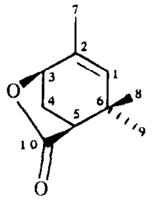
The presence of only one methyl singlet at δ0.91 required an unusual carbon skeleton. Additional information was provided by the observed NOE's Thus irradiation of the methyl singlet (H-14) had an effect on signals which must be due to H-2β, H-6, H-8β and H-9β and which had already been connected in the partial structures A and B. A NOE between H-7, H-13 and H-15 connected A and B with H-15 which itself showed a geminal coupling and NOEs with H-7 and H-9α. The latter showed an effect with H-1. These results required the proposed carbon skeleton with the assigned stereochemistry All data therefore agreed with the presence of an endoperoxide acetal. This was established by hydrogenation which gave the hydroxyketone **9** as followed from the ^{1}H and ^{13}C NMR spectra (Tables 2 and 3) On standing in $CDCl_3$, compound **9** was partly converted to the conjugated ketone **10**, its ^{1}H NMR data further supported the structures. The observed NOEs of **9** and **10** also established the proposed configurations of these lactones and indirectly that of the natural product which we have named tehranolide.

Most likely this unusual carbon skeleton was formed by oxidative cleavage of the Δ^4 bond of **2b** followed by an internal aldol condensation of the intermediate **5** affording the dihydroxy ketone **6**. The latter then could be rearranged to the lactone **7** by attack of HO^+ followed by acetal formation to give the lactone **8** (Scheme) A similar transformation was proposed for a ketone isolated from a *Jasonia* species [11].

EXPERIMENTAL

The air-dried aerial parts (400 g, collected 60 km N of Tehran, Iran, voucher deposited in the Herbarium of the Dept of Botany, Shahid Beheshty University, Tehran, Iran) were extracted with Et_2O–MeOH–petrol (1 1 1) The defatted extract (MeOH) was





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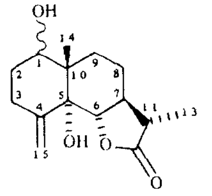
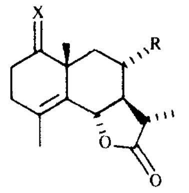
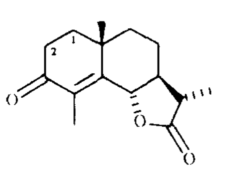


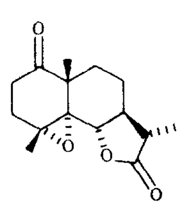
1a 1αOH
1b 1βOH



2a X = O R = OH
2b X = βOH H R = H



3a Δ^1
3b 1βOH



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separated first by CC (silica gel) into six fractions (1. Et_2O–petrol, 1·4, 2· Et_2O–petrol, 1:1, 3 Et_2O–petrol, 4 1, 4 Et_2O, 5 Et_2O–MeOH, 9 1 and 6 Et_2O–MeOH, 4·1). TLC of fraction 1 gave 50 mg phloroacetophenone dimethyl ether, 15 mg cycloartenone and 5 mg pinocarveol TLC of fraction 2 gave 10 mg filifolide A and of fraction 3 30 mg **1b** HPLC of fraction 4 (MeOH–H_2O, 3 2, always RP 8, flow rate, 3 ml/min) gave 27 mg **2b** (R_t 8 5 min) and 7 mg **4** HPLC of fraction 5 (MeOH–H_2O, 11 9) gave 8 5 mg **1a** (R_t 0 7 min), 20 mg **3a**, 11 mg **1b**, 5 mg **2a** HPLC of fraction 6 (MeOH–H_2O, 11 9) gave 10 mg **3b** (R_t 5 5 min) and 10 mg **8** (R_t 3 8 min) Known compounds were identified by comparing the 400 MHz ^1H NMR spectra with those of authentic material

1-epi-*Artemin* (**1a**) Colourless crystals, mp 188°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3570 (OH), 1775 (γ-lactone), MS *m/z* (rel int) 248 142 $[M-H_2O]^+$ (40) (calc for $C_{15}H_{20}O_3$ 248 141), 233 $[248-Me]^+$ (7), 230 $[248-H_2O]^+$ (10), 175 (30), 152 (42), 123 (72), 96 (62), 55 (100), $[\alpha]_D^{25°}$ −55 ($CHCl_3$, *c* 0 67)

1-epi-*Dehydroisoerivanin* (**3b**) Colourless crystal, mp 139°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3580 (OH), 1780 (γ-lactone), 1670 (C=CC=O), MS *m/z* (rel int) 264 136 $[M]^+$ (79) (calc for $C_{15}H_{20}O_4$ 264 136), 249 $[M-Me]^+$ (5), 246 $[M-H_2O]^+$ (4), 193 (39), 192 (71), 191 (100), 163 (56), 97 (58), 55 (88), $[\alpha]_D^{24}$ +43 ($CHCl_3$, *c* 0 2)

Tehranolide (**8**) Colourless crystals, mp 99°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3600 (OH), 1775 (γ-lactone), MS *m/z* (rel int) 280 $[M-H_2O]^+$ (2), 264 $[M-H_2O_2]^+$ (5), 246 $[264-H_2O]^+$ (14), 135 (31), 107 (56), 84 (96), 55 (100)

6 mg **8** in 5 ml Et_2O was hydrogenated in the presence of Pd/$BaSO_4$ (5%) TLC (Et_2O, two developments) gave **9** (R_f 0 25), colourless gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3520 (OH), 1785 (γ-lactone), 1715 (C=O), MS *m/z* (rel int) 282 147 $[M]^+$ (22) (calc for

Table 1. ^{1}H NMR spectral data of compounds **1a** and **3b** (400 MHz, $CDCl_3$, δ-values)

H	**1a**	**3b**
1	3.45 *br t*	3 87 *dd*
2	1.92 *dddd*	2 68 *dd*
2′	1.81 *dddd*	2.59 *dd*
3	2.90 *dtt*	—
3′	2.07 *ddd*	—
6	4 35 *d*	4.71 *dq*
7	2.33 *m*	1 64 *dq*
8	1.59 *m*	2.05 *dddd*
8′		1 91 *dq*
9	1 86 *m*	2.24 *ddd*
9′	1.29 *m*	1 45 *dt*
11	2.33 *m*	2.37 *dq*
13	1.23 *d*	1.28 *d*
14	1.34 *s*	1.29 *s*
15	5.14 *d* 5.08 *br s*	2.01 *d*

J[Hz]. Compound **1a**. 1,2 = 1,2′ = 2′,3′ = 3,15 = 3,15′ = 2.5, 2,2′ = 2,3 = 3,3′ = 14.5, 2,3′ = 4; 2′,3 = 5, 6,7 = 11.5; 11,13 = 7; compound **3b**: 1,2 = 5; 1,2′ = 13, 2,2′ = 16, 6,15 = 1.5, 6,7 = 7,8′ = 7,11 = 12; 7,8 = 3; 8,8′ = 8′,9′ = 9,9′ = 13; 8,9 = 8′,9 = 3; 8,9′ = 4.5; 11,13 = 7.

Table 2. ^{13}C NMR spectral data of compounds **8** and **9** (100 6 MHz, $CDCl_3$, δ-values)

C	**8***	**9***
1	80.9 *d*	79 8 *d*
2	24.6 *t*	21.9 *t*
3	33.8 *t*	35.2 *t*
4	93 8 *s*	81.5 *s*
5	105.6 *s*	205.2 *s*
6	84 7 *d*	83.3 *d*
7	50.5 *d*	51 9 *d*
8	29 6 *t*	22.7 *t*
9	37 7 *t*	28.2 *t*
10	50.1 *s*	40.1 *s*
11	43.1 *d*	42 1 *d*
12	175 9 *s*	177.3 *s*
13	12.2 *q*	12 5 *q*
14	12 6 *q*	13.4 *q*
15	50.1 *t*	54.5 *t*

*Assignments of the triplets may be interchangeable.

Table 3. ^{1}H NMR spectral data of compounds **8–10** (400 MHz, $CDCl_3$, δ-values)

H	**8** (MeOD)	**9**	**10**
1	3.40 *dd*	3.72 *t*	3 70 *dd*
2	1.78 *m*	2.04 *m*	2 03 *m*
2′	1.63 *m*	1.63 *m*	1 69 *dddd*
3	2.09 *m*	1.84 *m*	2 69 *ddt*
3′	1.80 *m*		2.48 *ddddd*
6	4 11 *d*	5.52 *d*	5.07 *d*
7	1.80 *dq*	1 87 *m*	1.96 *dq*
8	1.85 *m*	*	1.85 *m*
8′	1.53 *m*	*	*
9	1.96 *br dd*	2 01 *m*	*
9′	1.36 *br dd*	1.01 *br dd*	*
11	2 31 *dq*	2 30 *dq*	2 35 *dq*
13	1.21 *d*	1.22 *d*	1.28 *d*
14	0.91 *s*	1.07 *s*	1.17 *s*
15	2 98 *d*	2 80	5 99 *dt*
15′	2.30 *d*	2.72	

*Obscured.

J[Hz]: 6,7 = 11; 7,11 = 11; 11,13 = 7; compound **8**. 1,2 = 6; 1,2′ = 11; 7,8 = 11, 7,8′ = 1.5, 8,9 = 8, 8′,9′ = 12; 9,9′ = 15; 15,15′ = 14; compound **9**· 1,2 = 1,2′ = 8; 8′,9′ = 8; 9,9′ = 16; 15,15′ = 17; compound **10** 1,2 = 7, 1,2′ = 2,3′ = 11; 2,2′ = 13; 2,3 = 3,15 = 3′,15 = 2; 2′,3 = 10; 2′,3′ = 9; 3,3′ = 19; 7,8 = 11, 7,8′ = 3.5

$C_{15}H_{22}O_5$.282.147), 264 $[M-H_2O]^+$ (12), 246 $[264-H_2O]^+$ (4), 221 (71), 193 (100), 175 (37), 81 (76)

5 mg **9** on standing in $CDCl_3$ for 24 hr gave after TLC (Et_2O, two developments) 3 mg **10** (R_f 0.3), colourless gum; MS *m/z* (rel. int): 264.136 $[M]^+$ (18) (calc for $C_{15}H_{20}O_4$.264.136), 246 $[M-H_2O]^+$ (61), 190 (24), 121 (47), 107 (45), 81 (56), 55 (100).

Filifolide A (**11**). ^{1}H NMR (C_6D_6): δ 4.77 (*tq*, H-1), 3.89 (*dt*, H-3), 1.69 (*dt*, H-4), 1.47 (*d*, H-4′), 2.05 (*dt*, H-5), 1.45 (*d*, H-7), 1 10 (*s*, H-8), 0.70 (*s*, H-9); *J* [Hz]. 1,3 = 1,5 = 1,7 = 3,5 = 1.5, 3,4 = 4,5 = 5, 5,5′ = 11.5, ^{13}C NMR ($CDCl_3$) δ 176.3 *s*, 135 0 *s*, 132 8 *d*, 77 3 *d*, 48.7 *d*, 35.1 *s*, 33 5 *t*, 28.3 *q*, 27 1 *q*, 21.0 *q*.

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