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EUDESMANE DERIVATIVES AND HIGHLY OXYGENATED MONOTERPENES FROM IRANIAN *ARTEMISIA* SPECIES

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Key Word Index—*Artemisia tournefortiana*; *A. aucheri*; Compositae; sesquiterpenes; eudesmanolides; monoterpenes; geraniol derivatives.

Abstract—The aerial parts of *Artemisia tournefortiana* afforded three new eudesmanolides with a 12,6β-lactone ring and the corresponding acids which may be the precursors of the lactones. From *Artemisia aucheri* six highly oxygenated geraniol derivatives were isolated. The structures were elucidated by high field NMR techniques.

INTRODUCTION

The large genus *Artemisia* has been studied chemically by many groups. Most widespread in this genus are characteristic acetylenic compounds [1] and sesquiterpene lactones [2]. But also many other types of natural products have been reported from several species. In a continuation of our investigations of representatives of this genus from different parts of the world [3, 4], we have now studied the constituents of two species from Iran.

RESULTS AND DISCUSSION

The extract of the aerial parts of *Artemisia tournefortiana* Reichb. afforded the *cis,trans*-isomeric spiroketals **6** and **7** [5], ilicic acid, [6], the eudesmanolides **1–3** and the related acids **4** and **5**.

The main compound was the ketone **1** with the molecular formula $C_{15}H_{18}O_3$. Its IR spectrum indicated that a γ-lactone with an additional keto group was present (1760, 1710 cm^{-1}). Its ^1H NMR spectrum (Table 1) showed, in addition to the typical signals of the exomethylene group, only one low field signal at δ5.72. Spin decoupling indicated that the latter was due to H-6 as the vicinal proton (H-7) was coupled with H-13 and a pair of double doublets (H-8). The chemical shift of the latter signals required a neighbouring keto group. Furthermore, signals of an olefinic and quarternary methyl group were visible. All the data, therefore, were consistent with structure **1**. However, the stereochemistry had to be determined. The coupling $J_{6,7}$ agreed with the presence of a *trans*-lactone, but NOE difference spectroscopy clearly showed that **1** was a *cis*-lactone. Saturation of H-6 gave clear effects with H-7 (12%) and H-15 (10%). Further effects were observed between H-7, H-6 (10%) and H-8α (5%) as well as between H-15 and H-6 (12%). Thus the configuration at C-6 and the H-8 signals could be assigned. Also the ^{13}C NMR data agreed well with the proposed structure.

The ^1H NMR spectra of **2** and **3** (Table 1) were in part close to that of **1**. However, new low field signals (3.39 *dd* and 4.67 *dd*) indicated a changed situation. Spin decoupling showed the presence in both lactones of a 9β-oxygen function. Accordingly, **2** was a dihydro derivative of **1** and **3** the corresponding acetate. When the ^1H NMR signals of **1–3** were compared, it was obvious that the presence of a trigonal carbon in **1** caused a conformational change. Inspection of models showed that in the case of **1** a boat conformation was most likely with angles between H-6 and H-7 and H-7 and H-8α of nearly 0°, while in the lactones **2** and **3** these angles were slightly changed in agreement with reduced couplings for $J_{6,7}$ and $J_{7,8}$ as well as for $J_{7,13}$. The presence of identical configurations in the lactones **1** and **2** was established by the NOE's obtained with the alcohol **2**. Clear effects were observed between H-6, H-7 (7%) and H-15 (10%) as well as between H-9 and H-7 (3%). Accordingly, both H-6 and H-9 were α-orientated.

The ^1H NMR spectra of **4** and **5** (Table 1) were in part close to those of **1** and **3** respectively. However, the low field H-6 signal was missing and H-13 now displayed broadened singlets, typical for α-substituted acrylic acids. Treatment with diazomethane afforded the corresponding methyl ester of **4**. Spin decoupling allowed the assignment of all signals though those of H-2 and H-3 were overlapped multiplets. The ^{13}C NMR spectrum of **5** also supported the structure. Obviously **4** and **5** are precursors of **1** and **3** respectively. This may be responsible for the formation of the so far unobserved type of eudesmanolide with a Δ^4-double bond and a 6,12-*cis*-lactone. We have named the desoxo derivative of **1** tournefortiolide.

The aerial parts of *A. aucheri* Boiss. gave no sesquiterpenes but several highly oxygenated geraniol derivatives, the ketones **8–11**, the endoperoxides **12** and **13** as well as the acids **14** [7] and **15** [8].

The ^1H NMR spectrum of **8** (Table 2) showed an olefinic methyl singlet and a further 6H methyl singlet at δ1.37 indicating the presence of an dimethyl carbinol. Furthermore, an olefinic singlet at δ6.87 (2H) and a broadened triplet at δ6.71 (1H), which was coupled with a doublet at δ4.41 (2H), required an open chain monoter-

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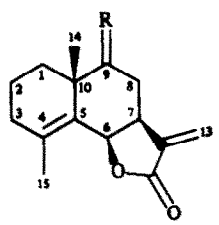
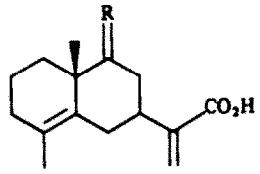


1 R = O
2 R = βOH,H
3 R = βOAc,H



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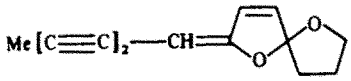
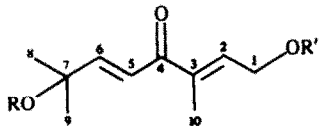
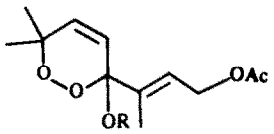
5 R = βOAc,H



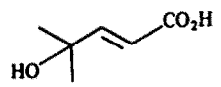
6 *E*
7 *Z*



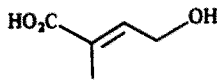
	8	9	9a	10	11
R	H	H	Ac	OH	OH
R'	H	Ac	Ac	H	Ac



12 R = H
13 R = Me



14



15

4a, **14a** and **15a** are the corresponding methylesters

pene, most likely derived from geraniol by allylic oxidation. Acetylation afforded **9**, which was also present in the extract and the diacetate **9a**. The ^{1}H NMR spectra (Table 2) were more informative, the olefinic singlet was replaced by a pair of doublets with a 15.5 Hz coupling and the broadened triplet at δ6.62 now showed clear allylic couplings with the olefinic methyl, which also was coupled with the methylene group (δ4.83). Accordingly, only the structures **8** and **9** agreed with all spectral data. The configuration of the Δ^2-double bond followed from a clear NOE between H-10 and H-1.

The ^{1}H NMR spectra of **10** and **11** (Table 2) were close to those of **8** and **9** respectively. However, the presence of the corresponding 7-hydroperoxy derivatives was indicated by the typical broadened singlets at δ7.72 and 7.76 respectively. Furthermore, the singlet at δ6.87 in the spectrum of **8** was replaced by a pair of doublets at δ6.90 and 6.82 in that of **10**.

The ^{1}H NMR spectral data of **12** and **13** (Table 2) differed considerably from those of **8**–**11**. A pair of olefinic doublets with a 10 Hz coupling indicated a *cis*-double bond. However, the chemical shifts of these signals were not in agreement with a *cis*-isomer of **10**. The methoxy signal in the spectrum of **13** required an acetal structure. Obviously **12** was the *cis*-isomer of **10**, but due to the changed stereochemistry a hemiacetal was formed, which was transformed to an acetal in the case of **13**. While EIMS gave no molecular ions, CIMS gave the required M + 1-peaks. The *E*-configuration of the Δ^2 double bond was determined by a clear NOE between H-10 and H-1. Most likely 4-oxo-geraniol is the common precursor for **8**–**13**. The spectral data of **14** and **15**, which were transformed to the methyl esters **14a** and **15a**, clearly led to the structures. Probably these acids are degradation products of **8**.

The constituents of these two *Artemisia* species from

Table 1. ^{1}H NMR spectral data of compounds 1–5 (400 MHz, $CDCl_3$, δ-values)

H	1	2	3	4a*	5
1α	1.70 *m*	1.30 *m*	1.25 *m*	1.59 *m*	1.37 *m*
1β	1.47 *m*	1.87 *m*	1.81 *m*	1.93 *m*	1.00 *m*
2	1.70 *m*	1.72 *m*	1.68 *m*	1.93 *m* 1.59 *m*	1.00 *m* 1.49 *m*
3	2.06 *dd*	2.13 *dd*	2.11 *dd*	1.93 *m*	1.95 *m* 1.60 *m*
6	5.72 *d*	5.21 *d*	5.22 *d*	2.20 *br dd* 2.86 *br d*	1.78 *br dd* 2.68 *br d*
7	3.64 *dddd*	3.06 *dddt*	3.13 *dddt*	2.73 *m*	2.52 *dddd*
8α	2.73 *dd*	1.90 *ddd*	1.94 *ddd*	2.45 *br d*	1.90 *br d*
8β	2.33 *dd*	1.72 *m*	1.78 *ddd*	2.70 *m*	1.71 *ddd*
9	—	3.39 *dd*	4.59 *dd*	—	4.67 *dd*
13	6.26 *d*	6.16 *d*	6.16 *d*	6.25 *br s*	6.36 *br s*
13'	5.62 *d*	5.61 *d*	5.59 *d*	5.61 *br s*	5.69 *br s*
14	1.09 *s*	1.05 *s*	1.12 *s*	1.30 *s*	1.10 *s*
15	1.80 *s*	1.80 *s*	1.81 *s*	1.69 *br s*	1.65 *br s*
OAc	—	—	2.07 *s*	—	2.05 *s*

*OMe: 3.78 *s*.

J[Hz]: Compound **1**: 2,3 = 5; 2',3 = 8; 6,7 = 9; 7,8α = 7.5; 7,8β = 2.5; 7,13 = 3; 7,13' = 2.5; 8α,8β = 14; compounds **2** and **3**: 2,3 = 5; 2',3 = 7; 6,7 = 6; 7,8α = 7; 7,8β = 11; 7,13 = 1.5; 8α,8β = 8β,9α = 12; 8α,9α = 4; compound **4**: 6,6' = 13; 6,7 ~ 10; 6',7 = 6; 7,8α ~ 3; 7,8β ~ 10; 8α,8β ~ 12; compound **5**: 6,6' = 6',7 = 7,8β = 8α,8β ~ 12; 6,7 = 7,8α = 3.

Table 2. ^{1}H NMR spectral data of compounds **8**–**13** and **9a** (400 MHz, $CDCl_3$, δ-values)

H	8	9	9a	10	11	12	13*
1 1'	4.41 *br d*	4.82 *dq*	4.82 *dq*	4.48 *br d*	4.83 *dq*	4.69 *dd* 4.64 *dd*	4.68 *dd* 4.63 *dd*
2	6.71 *br t*	6.61 *tq*	6.55 *tq*	6.71 *br t*	6.60 *tq*	6.11 *tq*	5.92 *tq*
5	6.87 *s*	6.86 *d*	6.60 *d*	6.82 *d*	6.77 *d*	5.73 *d*	5.66 *d*
6		6.93 *d*	6.91 *d*	6.90 *d*	6.90 *d*	6.01 *d*	6.04 *d*
8 9	1.37 *s*	1.39 *s*	1.57 *s*	1.43 *s*	1.43 *s*	1.28 *s* 1.45 *s*	1.29 *s* 1.42 *s*
10	1.78 *br s*	1.88 *dt*	1.88 *dt*	1.84 *br s*	1.89 *dt*	1.74 *br s*	1.73 *br s*
OAc	—	2.10 *s*	2.12,2.04 *s*	2.13 *s*	2.13 *s*	2.07 *s*	2.07 *s*
OOH			—	7.72 *br s*	7.76 *br s*		

*OMe: 3.38 *s*;

J[Hz]: Compounds **8**–**11**: 1,2 = 6; 1,10 = 1; 5,6 = 16; compounds **12** and **13**: 1,1' = 14; 1,2 = 1',2 = 6.5; 1,10 = 2,10 = 1; 5,6 = 10.

Iran show that they are not closely related. Further investigations may show whether the observed types of natural products are of chemotaxonomic relevance. Already now there are indications that a differentiation of *Artemisia* species by their chemistry will be very useful. So far the majority contain sesquiterpene lactones and acetylenic compounds of different types but some species do not contain these compounds which in part are replaced by unusual monoterpenes.

EXPERIMENTAL

The air dried plant material was extracted with MeOH–Et_2O–petrol (1:1:1) and worked-up as reported previously [9]. The extract of the aerial parts of *A. tournefortiana* (250 g, collected 90 km South of the Caspian Sea, Heraz Road, Iran, vouchers always deposited in the Herbarium of the Dept. of Botany, University of Tehran, Iran) was first separated by CC (Silica gel). The polar fractions (Et_2O-petrol, 1:1 and Et_2O) were further separated by PTLC (Silica gel, PF 254) affording 15 mg **3** (Et_2O–petrol, 1:1, R_f 0.40), 10 mg **5** (Et_2O–petrol, 7:3, R_f 0.75), 200 mg **1** (Et_2O–petrol, 7:3, R_f 0.45), 10 mg **4** (Et_2O–petrol, 7:3, R_f 0.7), purified as its methyl ester, and 20 mg **2** (Et_2O–C_6H_6, 3:2, R_f 0.25). The less polar CC fractions gave by PTLC 45 mg **6**, 30 mg **7** and 60 mg illicic acid. The 400 MHz ^{1}H NMR spectra of compounds **6**–**8** were identical with those of authentic material.

The extract of the aerial parts of *A. aucheri* (200 g, collected 60 km south of Shiraz, Iran) was separated by CC. The fractions

obtained with Et_2O–petrol (1:1) gave by PTLC (Et_2O–petrol, 3:2) 10 mg **13** (R_f 0.47) and the fractions obtained with Et_2O afforded by PTLC 80 mg **8** (Et_2O–petrol, 9:1, R_f 0.50), 12 mg **9** (Et_2O–petrol, 7:3, R_f 0.45), 8 mg **10** (Et_2O–petrol, 4:1, R_f 0.38), 15 mg **11** (Et_2O–petrol, 7:3, R_f 0.35), 5 mg **12** (HPLC, RP 8, MeOH–H_2O, 11:9, R_t 9 min.), 5 mg **14** and **15** which were separated as their methyl esters **14a** and **15a**.

9-Oxo-tournefortiolide (**1**). Colourless crystals, mp 165°; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 1760 (γ-lactone), 1710 (C=O); MS *m/z* (rel. int.): 246.126 $[M]^+$ (100) (calc. for $C_{15}H_{18}O_3$: 246.126), 231 $[M - Me]^+$ (47), 203 $[231 - CO]^+$ (78), 185 $[203 - H_2O]^+$ (28), 157 (26), 131 (28), 91 (26); ^{13}C NMR ($CDCl_3$, C-1 – C-15): 34.0 *t*, 17.6 *t* 32.1 *t*, 128.1 *s*, 137.8 *s*, 75.1 *d*, 37.3 *d*, 40.8 *t*, 213.3 *s*, 47.0 *s*, 139.6 *s*, 169.4 *s*, 123.9 *t*, 19.4 *q*, 24.4 *q*; $[\alpha]_D^{24°} + 44$ ($CHCl_3$; *c* 2.2).

9β-Hydroxytournefortiolide (**2**). Colourless oil; IR $\nu_{max}^{CCl_4}$, cm^{-1}: 3550 (OH), 1770 (γ-lactone); MS *m/z* (rel. int.): 248.141 $[M]^+$ (24) (calc. for $C_{15}H_{20}O_3$: 248.141), 233 $[M - Me]^+$ (12), 230 $[M - H_2O]^+$ (63), 215 $[230 - Me]^+$ (20), 204 $[M - C_2H_4O]^+$ (52), 139 (100); $[\alpha]_D^{24°} - 12$ ($CHCl_3$; *c* 0.6).

9β-Acetoxytournefortiolide (**3**). Colourless oil; IR $\nu_{max}^{CCl_4}$, cm^{-1}: 1770 (γ-lactone), 1740 (OAc); MS *m/z* (rel. int.): 290.152 $[M]^+$ (32) (calc. for $C_{17}H_{22}O_4$: 290.152), 275 $[M - Me]^+$ (12), 248 $[M$ – ketene$]^+$ (13), 230 $[M - HOAc]^+$ (100), 215 $[230 - Me]^+$ (46), 204 $[248 - C_2H_4O]^+$ (30); $[\alpha]_D^{24°} + 14$ ($CHCl_3$; *c* 0.2).

9-Oxo-4,5-dehydro-4(15)-dihydrocostic acid methyl ester (**4a**). Colourless oil; IR $\nu_{max}^{CCl_4}$, cm^{-1}: 1740 (CO_2R), 1710 (C=O); MS *m/z* (rel. int.): 262.157 $[M]^+$ (60) (calc. for $C_{16}H_{22}O_3$: 262.156), 247 $[M - Me]^+$ (18), 244 $[M - H_2O]^+$ (38), 220 $[M - C_2H_2O]^+$ (55), 133 (100); $[\alpha]_D^{24°} - 24$ ($CHCl_3$; *c* 0.3).

9β-Acetoxy-4,5-dehydro-4(15)-dihydrocostic acid (**5**). Colourless oil; IR $\nu_{max}^{CCl_4}$, cm^{-1}: 3500–2600, 1700, 1620 (C = CCO_2H), 1740 (OAc); MS *m/z* (rel. int.): 292.167 $[M]^+$ (**14**) (calc. for $C_{17}H_{24}O_4$: 292.167), 232 $[M - HOAc]^+$ (100), 217 $[232 - Me]^+$ (25); ^{13}C NMR ($CDCl_3$, C-1–C-15): 30.7 *t*, 18.5 *t*, 32.2 *t*, 143.4 *s*, 129.0 *s* 32.9 *t*, 37.1 *d*, 35.7 *t*, 79.9 *d*, 39.1 *s*, 131.6 *s*, 170.8 *s*, 125.5 *t*, 19.0 *q*, 19.8 *q*; OAc: 171.8 *s*, 21.2 *q*; $[\alpha]_D^{24°} + 48$ ($CHCl_3$; *c* 0.3).

3,7-Dimethyl-1,7-dihydroxy-octa-2E,5E-dien-4-one (**8**). Colourless oil; IR $\nu_{max}^{CCl_4}$, cm^{-1}: 3610 (OH), 1665, 1620 (C=CCOC=C); CIMS *m/z* (rel. int.): 185 $[M + 1]^+$ (20), 167 $[185 - H_2O]^+$ (46), 149 $[167 - H_2O]^+$ (100), 127 $[185 - Me_2CO]^+$ (57). Acetylation (Ac_2O, 3 hr, 75°) afforded **9**, identical with the natural acetate, and **9a**; MS *m/z* (rel. int.): 268.131 $[M]^+$ (2.5) (calc. for $C_{14}H_{20}O_5$: 268.131), 209 $[M - OAc]^+$ (72), 149 $[209 - HOAc]^+$ (100).

1-Acetoxy-3,7-dimethyl-7-hydroxy-octa-2E,5E-dien-4-one (**9**). Colourless oil; IR $\nu_{max}^{CCl_4}$, cm^{-1}: 3600 (OH), 1740 (OAc), 1665 (C =CCOC=C); MS *m/z* (rel. int.): 226 $[M]^+$ (0.5), 167 $[M - OAc]^+$ (44), 166.099 $[M - HOAc]^+$ (20) (calc. for $C_{10}H_{14}O_2$: 166.099), 151 (39), 123 (60), 113 $[HOC(Me)_2CH{=}CHCO]^+$ (25), 95 $[113 - H_2O]^+$ (100).

3,7-Dimethyl-1-hydroxy-7-peroxy-octa-2E,5E-dien-4-one (**10**). Colourless oil; CIMS *m/z* (rel. int.): 201 $[M + 1]^+$ (72), 183 $[201 - H_2O]^+$ (100), 167 $[201 - H_2O_2]^+$ (44), 165 $[183 - H_2O]^+$ (43), 127 (56).

1-Acetoxy-3,7-dimethyl-7-peroxy-octa-2E,5E-dien-4-one (**11**). Colourless oil; CIMS *m/z* (rel. int.): 243 $[M + 1]^+$ (21), 225 $[243 - H_2O]^+$ (81), 209 $[243 - H_2O_2]^+$ (38), 183 $[243 - HOAc]^+$ (32), 149 $[183 - H_2O_2]^+$ (100).

1-Acetoxy-3-7-dimethyl-4-hydroxy-octa-2E,5Z-dien-4,7-endo-peroxide (**12**). Colourless oil; CIMS *m/z* (rel. int.): 243 $[M + 1]^+$ (1), 225 $[243 - H_2O]^+$ (31), 165 $[225 - HOAc]^+$ (58), 123 (100).

1-Acetoxy-3,7-Dimethyl-4-methoxy-octa-2E,5Z-dien-4,7-endo-peroxide (**13**). Colourless oil; MS *m/z* (rel. int.): 224 $[M - O_2]^+$ (78), 164 $[224 - HOAc]^+$ (72), 149 $[164 - Me]^+$ (100); CIMS *m/z* (rel. int.): 257 $[M + 1]^+$ (1.3), 225 $[257 - O_2]^+$ (30), 197 (2), 165 (61), 123 (100).

Methyl-4-hydroxy-4-methyl-pent-2E-enoate (**14a**). Colourless oil; MS *m/z* (rel. int.): 129 $[M - Me]^+$ (58), 113 $[M - OMe]^+$ (21), 101 $[129 - CO]^+$ (100); ^1H NMR ($CDCl_3$): 6.04 (*d*, H-2), 7.02 (*d*, H-3), 1.38 (*s*, H-5, H-6), 3.75 (*s*, OMe) (*J* [HZ]: 2,3 = 15.5).

Methyl-4-hydroxytiglate (**15a**). Colourless oil; MS *m/z* (rel. int.): 101 $[M - OMe]^+$ (100); ^1H NMR ($CDCl_3$): 6.83 (*tq*, H-3), 4.38 (*dq*, H-4), 1.85 (*dt*, H-5), 3.76 (*s*, OMe) (*J* [Hz]: 3,4 = 6; 3,5 = 4,5 = 1.5).

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REFERENCES

1. Bohlmann, F., Burkhardt, T. and Zdero, C. (1973) *Naturally Occurring Acetylenes*. Academic Press, London.
2. Seaman, F. C. (1982) *Bot. Rev.* **48**, 217.
3. Jakupovic, J., Chau-Thi, T. V., Warning, U., Bohlmann, F. and Greger, H. (1986) *Phytochemistry* **25**, 1663.
4. Greger, H., Zdero, C. and Bohlmann, F. (1986) *Phytochemistry* **25**, 891.
5. Bohlmann, F., Herbst, P., Arndt, C., Schönowski, H. and Gleinig, H. (1961) *Chem. Ber.* **94**, 3193.
6. Herz, W., Chikematsu, H. and Tether, L. R. (1966) *J. Org. Chem.* **31**, 1632.
7. Agarwal, S. G., Thappa, R. K., Dhar, K. L. and Atal, C. K. (1981) *Indian J. Chem.* **20**, 164.
8. Löffler, A., Pratt, R. J., Rüesch, H. P. and Dreiding, A. S. (1970) *Helv. Chim. Acta Scand.* **53**, 383.
9. Bohlmann, F., Zdero, C., King, R. M. and Robinson, H. (1984) *Phytochemistry* **23**, 1979.