Pergamon

Phytochemistry, Vol. 45, No. 1, pp. 107–109, 1997
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0031-9422/97 $17.00+0.00

PII: S0031-9422(96)00790-X

SESQUITERPENOIDS FROM *TANACETUM ARGENTEUM* SUBSP. *CANUM* VAR. *CANUM**

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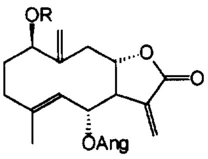
(*Received in revised form* 16 *October* 1996)

Key Word Index—*Tanacetum argenteum* subsp. *canum* var. *canum*; Compositae; sesquiterpene lactones; eudesmanolides; germacranolides; guaianolides.

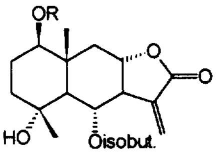
Abstract—Aerial parts of *Tanacetum argenteum* subsp. *canum* var. *canum* afforded fourteen sesquiterpene lactones, two of them being new. The new compounds 1*β*-hydroxy-6*α*-angeloyloxygermacra-4(5),10(14),11(13)-trien-8,12-olide and 1*β*,4*α*-dihydroxy-6*α*-isobutyloxyeudesm-11(13)-en-8,12-olide, as well as the known ones: parthenolide, peroxyparthenolide, dihyroparthenolide, 1-*epi*-tatridin B, sivasinolide, flabellin, 1*β*,4*α*-dihydroxy-6*α*-angeloyloxyeudesm-11(13)-en-8,12-olide, 1*β*-hydroxy-6*α*-angeloyloxyeudesm-4(15),11(13)-dien-8,12-olide, michelenolide, magnograndiolide, santamarin and douglanin, were identified by spectral methods.

INTRODUCTION

Tanacetum argenteum has three subspecies in Turkey, *T. argenteum* ssp. *argenteum*, ssp. *flabellifolium* and ssp. *canum*, two of them being endemic. The last species is further classified into two varieties, var. *canum* and var. *pumilum* [1]. In this paper, we wish to report the constituents of *T. argenteum* subsp. *canum* var. *canum*.



1 : R=H
1a : R=OAc



2 : R=H
2a : R=OAc

RESULTS AND DISCUSSION

The aerial parts of *T. argenteum* (Lam.) Wild., subsp. *canum* (C. Koch) Grierson var. *canum* yielded 12 known and two new sesquiterpenoids. The known compounds are parthenolide [**3**][2], peroxyparthenolide [**4**][3], dihydroparthenolide [**5**][4], 1-*epi*-tatridin B [**6**][5], sivasinolide [**7**][6], flabellin [**8**][7], 1*β*,4*α*-dihydroxy-6*α*-angeloyloxyeudesm-11(13)-en-8,12-olide [**9**][8], 1*β*-hydroxy-6*α*-angeloyloxyeudesm-4(15),11(13)-dien-8,12-olide [**10**][9], michelenolide [**11**][10], magnograndiolide [**12**][11], santamarin [**13**][12], douglanin [**14**][13], and the new ones: 1*β*-hydroxy-6*α*-angeloyloxygermacra-4(5),10(14),11(13)-trien-8,12-olide [**1**] and 1*β*,4*α*-dihydroxy-6*α*-isobutyloxyeudesm-11(13)-en-8,12-olide [**2**].

The CIMS spectrum of **1** gave a molecular peak at m/z 346.9 $[M^+]$ corresponding to the molecular formula $C_{20}H_{26}O_5$. The ^1H NMR spectrum of the compound (Table 1) displayed exocyclic methylene protons of the lactone ring at δ 6.34 ($J = 3.5$ Hz) and at δ 5.88 ($J = 3.0$ Hz). The olefinic methyl signal δ 1.85 (*d*, $J = 1.5$ Hz), the second exocyclic methylene signals at δ 5.17 (*br s*) and 5.02 (*br s*) and a broadened doublet at δ 4.78 (H-5), indicated a germacranolide. The appearance of H-6 in lower field at δ 5.34 (*dd*, $J = 10$, 10 Hz) implied an ester group located at C-6. The quartets of quartet at δ 6.13 and olefinic methyl signals at δ 1.94 (*dq*, $J = 7.5$, 1.5 Hz) and 1.89 (*br s*) showed that the ester was an angeloyloxy group. The protons were assigned by spin decoupling experiments. The APT spectrum of **1** gave three methyl signals, two olefinic and three saturated methylene signals, five methine signals two of them being olefinic, two methine carbons bounded to an oxygen function, four olefinic quarternary carbon signals and a carbonyl signal (Table 2). Acetylation of the compound yielded a monoacetate (**1a**) giving a signal at δ 2.07 and a multiplet at δ 5.54 which yielded a better dispersion in

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* Dedicated to Prof. Ayhan Ulubelen (University of Istanbul, Turkey) on the occasion of her sixty-fifth birthday.

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Table 1. ^{1}H NMR data of **1–2** (200 MHz, a = $CDCl_3$, b = C_6D_6, c = d_6-acetone)

	1^a	**1**^{b}	**1**^{c}	**1a**^{a}	**1a**^{b}	**2**^{a}	**2**^{b}	**2**^{c}	**2a**^{a}
H-1	4.10*m*	3.77 *m*	3.59*m*	5.54*m*	5.58*dd*	3.48*m*	2.83*m*	3.44*m*	4.67*dd*
H-2							1.18*m*	1.65*m*	1.55*m*
H-3							1.02*m*	1.44*m*	
H-5	4.78*d*	4.68*d*	4.98*d*	4.96*br d*	4.73*d*		1.20*d*	1.87*d*	1.82*m*
H-6	5.34*dd*	5.29*dd*	5.53*dd*	5.38*dd*	5.23*dd*	5.70*dd*	5.51*dd*	5.66*dd*	5.70*dd*
H-7	3.08*m*	2.61*m*	3.22*dddd*	3.07*dddd*	2.05*m*	2.85*br dd*	2.33*dddd*	2.90*dddd*	2.84*ddd*
H-8	4.20*m*	3.77*m*	4.18*m*	4.22*m*	3.95*m*	4.03*ddd*	3.45*ddd*	4.13*ddd*	4.01*ddd*
H-9	3.08*m*	2.10*dd*	2.50*dd*	2.60*dd*	2.20*dd*		2.22*dd*	2.48*dd*	2.12*dd*
H-9′							1.06*d*	1.50*d*	1.55*m*
H-13	6.34*d*	6.31*d*	6.14*d*	6.34*d*	6.34*d*	6.09*d*	6.07*d*	5.91*d*	6.09*d*
H-13′	5.88*d*	5.66*d*	5.79*d*	5.86*d*	5.64*d*	5.30*d*	5.23*d*	5.28*d*	5.31*d*
H-14	5.17*br s*	4.56*br s*	5.16*br s*	5.25*br s*	4.75*br s*	1.04*s*	0.47*s*	1.02*s*	1.02*s*
H-14′	5.02*br s*	4.56*br s*	5.09*br s*		4.61*br s*				
H-15	1.85*d*	1.78*d*	1.90*dq*	1.80*br s*	1.61*d*		1.07*s*	1.23*s*	1.28*s*
H-2′			1.94*dq*			2.56*m*	2.33*m*	2.50*m*	2.59*ddd*
H-3′	6.13*qq*	5.72*qq*		6.15*qq*	5.71*qq*		0.91*d*	1.12*d*	1.21*d*
H-4′	1.89*br s*	1.80*dq*		1.86*dq*	1.75*dq*		1.03*d*	1.26*d*	1.23*d*
H-5′	1.94*dq*	1.92*dq*		1.93*dq*	1.90*dq*				
OH	3.60*br d*								
OAc				2.07*s*	1.63*s*				2.07*s*

J(Hz): **1**: 5,6 = 6,7 = 10; 7,8 = 8; 8,9 = 5.5; 8,9′ = 14; 7,13 = 3.5; 7,13′ = 3; 15,5 = 1.5; 3′,4′ = 7; 3′,5′ = 4′,5′ = 1.5; **2**: 1,2 = 4.5; 1,2′ = 10; 5,6 = 6,7 = 10; 8,9 = 4; 8,9′ = 7,8 = 13; 7,13 = 3.5; 7,13′ = 3; 2′,3′ = 2′,4′ = 6.5.

Table 2. ^{13}C NMR data of **1–2** (50.75 MHz, $CDCl_3$)

	1	2
C-1	78.6(−)	77.6(−)
C-2	29.6(+)	27.9(+)
C-3	45.9(+)	41.6(+)
C-4	145.0(+)	72.0(+)
C-5	139.0(−)	57.2(−)
C-6	71.9(−)	69.7(−)
C-7	49.0(−)	52.8(−)
C-8	75.1(−)	75.9(−)
C-9	42.6(+)	45.1(+)
C-10	136.5(+)	41.0(+)
C-11	135.9(+)	126.1(+)
C-12	170.9(+)	138.0(+)
C-13	116.6(+)	117.3(+)
C-14	125.2(+)	15.8(−)
C-15	15.7(−)	21.4(−)
C-1′	168.0(+)	*
C-2′	127.1(+)	34.6(−)
C-3′	129.6(−)	18.5(−)
C-4′	18.6(−)	19.0(−)
C-5′	20.4(−)	

*Not observed.

C_6D_6 at 5.58 (*dd*, *J* = 5.5, 10.5 Hz). The H-1 signal at δ 4.10 (*m*) was shifted to 5.54 in the spectrum of the acetate and the broadened doublet at δ 3.60 (OH) disappeared. The signals were assigned by spin decoupling experiments. HRMS spectrum of **1a** gave a molecular peak at *m/z* 388.1889 $[M]^+$ corresponding to $C_{22}H_{28}O_6$.

The CIMS spectrum of **2** gave a molecular ion peak at *m/z* 353 corresponding to the molecular formula $C_{19}H_{29}O_6$ $[M+1]^+$. The HRMS spectrum run in Cl technique, gave the molecular ion peak at *m/z* 353.19413. The ^{1}H NMR spectrum in $CDCl_3$ (Table 1) exhibited exocyclic methylene protons at δ 6.09 (H-13, *d*, *J* = 3.5 Hz) and 5.30 (H-13′, *d*, *J* = 3.0 Hz). The methyl singlets at δ 1.02 (H-14) and 1.26 (H-15), the threefold doublet at 4.03 (H-8, *ddd*, *J* = 3.5, 10, 10 Hz) and the double doublet at δ 5.70 (H-6, *dd*, *J* = 10, 10 Hz) indicated an 8,12-lactonised eudesmanolide having an ester group at C-6. The broadened multiplet at δ 3.48 indicated a hydroxyl group at C-1; however, because of the overlapping signals at δ 1.21 and [illegible] 91, ester protons could not be observed clearly. The ^{1}H NMR spectrum in C_6D_6 (Table 1) gave a better dispersion. Two secondary methyl doublets appeared at δ 1.07 (*J* = 6 Hz) and 0.94 (*J* = 6 Hz) in this spectrum indicating an isobutyl ester group at C-6. Acetylation of the compound caused the H-1 proton shift from δ 3.48 to 4.67 and an acetyl signal was observed at δ 2.07 in the ^{1}H NMR spectrum of **2a**. All the signals were assigned by spin decoupling experiments. The APT spectrum of **2** supported the structure giving three oxygenated methine signals, an oxygenated quarternary carbon signal, four methyl signals, an olefinic methylene signal and the other signals of the molecule (Table 2). The proton bearing carbon signals were assigned by HETCOR spectrum. The configuration of the hydroxyl group at C-4 was deduced by comparing chemical shifts with those of similar compounds [14].

EXPERIMENTAL

General. Kieselgel 60 (0.063–0.200 mm, Merck) and Sephadex LH-20 (Pharmacia); TLC precoated silica gel 60 F_{254}, 0.2 mm plates (Merck), spots were detected under UV and by spraying acidified ceric sulphate followed by heating. ^{1}H NMR operating at 200 MHz; ^{13}C NMR, operating at 50.32 MHz, with $CDCl_3$, C_6D_6, d_6-acetone as solvents and TMS as int. standard.

Plant material. Tanacetum argenteum (Lam.) Wild., subsp. *canum* (C. Koch) Grierson var. *canum* was collected from Southeast Taurus Mountains (Gülek Tepe-Adana). A voucher specimen (ISTE 64366) was deposited in the Herbarium of the Faculty of Pharmacy, University of Istanbul, Turkey.

Extraction and isolation. Dried and powdered aerial parts (1 kg) were extracted successively with petrol (bp 40–60°), ethyl acetate and MeOH. The ethyl acetate and MeOH extracts (60 g) were combined and treated with MeOH. The residue was applied to a silica gel column and eluted with petrol with a gradient of dichloromethane, EtOAc, Me_2CO and MeOH. The fractions from CC were controlled by TLC and the similar frs were combined and further separated on silica gel columns and by prep. TLC. Thus, 8 mg **1**, 12 mg **2**, 575 mg **3**, 16 mg, **4**, 60 mg **5**, 5 mg **6** 4.5 mg **7**, 315 mg **8**, 15 mg **9**, 8.5 mg **10**, 13 mg **11**, 6 mg **12**, 84 mg **13**, 109 mg **14**, were obtained.

1β-*Hydroxy*-6α-*angeloyloxygermacra*-4(5),10(14),11 (13)-*trien*-8,12-*olide* [**1**]: IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3400 (OH), 1750 (α,β-unsaturated-γ-lactone), 1740, (ester), 1650 (unsaturation). ^{1}H and ^{13}C NMR given in Tables 1 and 2, respectively.

Acetate of **1** [**1a**]: IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1750, 1740, 1730, 1650, 1260 ^{1}H and given in Table 1. HRMS *m/z* for $C_{22}H_{28}O_6$ (calc. 388.1884, obs. 388.1889); CIMS *m/z* 388 $[M]^+$, 387 $[M-1]^+$. EIMS *m/z* (rel. int.): 387 $[M-1]^+$(55), 287 [M – angelic acid]$^+$ (21), 244 $[287-CH_3COO]^+$(100), 227 $[287-CH_3COOH]^+$(56), 199 $[277-CO]^+$(30), 173 (25), 133 (26), 105 (42), 91 (59), 83 (70).

1β, 4α-*Dihydroxy*-6α-*isobutyloxyeudesm*-11 (13)-*en*-8,12-*olide* [**2**]: IR $\nu_{\max}$ cm^{-1}: 3480 (OH), 1770 (α,β-unsaturated-γ-lactone), 1720, 1260 (ester), 1680 (C=C). ^{1}H and ^{13}C NMR given in Tables 1 and 2, respectively. CIMS *m/z* 353 for $(C_{19}H_{29}O_6)$ $[M+1]^+$. HRMS *m/z* for $C_{19}H_{29}O_6$ (Calc. 353.19624, obs. 353.19413). EIMS *m/z* (rel. int.): 352 $(C_{19}H_{28}O_6)$ $[M]^+$(6), 337 $[M-CH_3]^+$(12), 264 $[M-HOOC\text{-}(CH)Me_2]^+$(36), 249 $[264-CH_3]^+$(40), 231 $[249-H_2O]^+$(54), 213 $[231-H_2O]^+$ (56), 202 (69), 188 (80), 165 (95), 146 (92), 125 (100), 108 (96), 79 (94).

Acknowledgements—The authors thank Prof. Dr N. Özhatay (Istanbul, Turkey) for identification of the plant, and the Department of Forestry in Gülek Tepe for their help in locating and collecting the plant.

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