Pergamon

0031-9422(95)00344-4

Phytochemistry, Vol. 40, No. 3, pp. 875-879, 1995

0031-9422/95 $9.50 + 0.00

PERSIANONE, A DIMERIC DITERPENE FROM *BALLOTA AUCHERI*

A. RUSTAIYAN, M. H. MOSSLEMIN-KUPAII, F. PAPASTERGIOU* and J. JAKUPOVIC*

Department of Chemistry, Shahid Beheshty University, Eveen, Tehran, Iran; *Institute for Organic Chemistry, Technical University of Berlin, D-10236 Berlin, Germany

(*Received in revised form* 22 *March* 1995)

Key Word Index—*Ballota aucheri*; Labiatae; diterpenes; labdanes; seco-labdane; dimeric labdane.

Abstract—The aerial parts of *Ballota aucheri* contained, in addition to known compounds, three new diterpenes. The structures were elucidated by high field NMR spectroscopy and chemical transformations.

INTRODUCTION

Recently we reported on the isolation of several new diterpenes from *Ballota aucheri* Boiss (tribe Stachydiodeae) [1]. The genus is characterized by the occurrence of furolabdanes and furoclerodanes [2–5]. We now report on the isolation of further diterpenes from *B. aucheri*.

RESULTS AND DISCUSSION

The aerial parts of *B. aucheri* contained, in addition to the known diterpenes **1** [2] and **2** [1], a further furolabdane (**3**), the seco derivative **4** as well as the dimer **5**.

The ^{1}H NMR spectrum of **3** showed signals typical of a β-substituted furan ring (Table 1), and four tertiary methyl signals pointed to a labdane skeleton. A doublet of doublet at δ4.34 (H-6), which was coupled with a methine doublet at δ1.54 (H-5) and a D_2O-exchangeable signal at δ3.32 supported an axially oriented secondary hydroxy group. That ring A was not functionalized was indicated by three consecutive methylene groups. The ^{13}C NMR spectrum (Table 2) contained signals for a double bond and a keto group. The chemical shift of the latter was in accordance with a conjugated ketone. Thus, the structure **3** was likely and final confirmation was achieved by 2D hetero and homo COSY experiments. NOE difference spectroscopy was also helpful for assignment of methyl signals. Important NOEs were observed between H-18, H-19, H-5 (7%) and H-6 (12%) as well as between OH, H-6 (5%) and both axial methyl groups H-19 and H-20.

The ^{1}H NMR spectrum of **4** was in part similar to that of **3** (Table 1). Again a β-substituted furan ring and the sequences H-1–H-3 and H-11–H-12 were present, but now only three tertiary methyl signals were observed. The most striking signals were those for an ethyl group, a structural feature not very common among diterpenes. Further information came from the ^{13}C NMR spectrum (Table 2), which showed a keto group and a singlet at δ108.0 suggestive of an acetal carbon. Furthermore, a doublet at δ81.8 required an additional oxygen-bearing tertiary carbon. A corresponding signal in the ^{1}H NMR spectrum at δ4.25 appeared as a doublet and was coupled with a doublet at δ2.29 (H-5). A sharp singlet at δ3.01 was due to a tertiary hydroxyl group. Taking into account all of these facts the structure **4** was likely. The stereochemistry followed from the results of NOE experiments. Effects were observed between H-18, H-5 (7%), H-3α (5%), H-3β (3%), H-8 (1.5%), H-6 (2%) and H-19, between H-19/20 and H-18, H-2, H-11 and H-6 (13%) and between OH and H-5 (5%). The large coupling $J_{5,6\beta} = 11.5$ Hz supported the *trans*-diaxial orientation of the corresponding hydrogens. The formation of this unusual compound could be easily explained in term of a retro aldol reaction starting from a derivative of **1** having a tertiary hydroxyl group at C-9 and subsequent formation of the hemiacetal between a newly formed keto group at C-9 and the hydroxy group at C-6.

The ^{1}H NMR spectrum of compound **5** (Table 1) showed two sets of signals indicating a dimeric structure. By a combination of 2D homo and hetero COSY experiments, the positions of all the signals were localized and assigned to two furolabdane subunits. The ^{1}H- and ^{13}C NMR signals (Tables 1 and 2) for the subunit A (Scheme 1) resembled those of compound **2** [1]. However, several of the assignments of ^{13}C NMR signals have to be corrected [1]. For the sake of comparison, the corrected data are added in Table 2. The difference in the chemical shifts of C-7 in compounds **2** and **5** (12.1 ppm) indicated that the connecting carbons in the dimer were probably joined by an ether linkage. The second subunit (B) gave rise to ^{13}C NMR signals for a tetrasubstituted double bond, a keto group and an oxygen-bearing carbon, the latter being the coupling position to the subunit (A). As both H-5 and H-7 appeared as singlets, the keto group had to be placed at C-7. Thus, an ether bond betweeen C-7 of both subunits was likely. This assumption was confirmed by a 2D long range hetero correlation

Table 1. ^{1}H NMR data for compounds **3**–**5** ($CDCl_3$, 400 MHz)

			5	
H	**3**	**4**	A	B
1α	1.34 *br ddd*	1.65 *m**	1.65 *m*	1.49 *m*
1β	1.91 *br dd*	1.48 *m**	1.47 *m*	1.92 *m*
2α	1.59 *ddddd*	1.60 *m**	1.70 –	1.70 –
2β	1.82 *ddddd*		1.45 *m*	1.45 *m*
3α	1.21 *br ddd*	1.13 *m**	1.06 *br ddd*	1.17 *br ddd*
3β	1.43 *br ddd*	1.43 *m**	1.23 *m*	1.31 *br ddd*
5	1.54 *d*	2.29 *d*	2.90 *br s*	2.70 *br s*
6	4.34 *dd*	4.25 *d*	—	—
7			3.43 *dd*	2.83 *br s*
8		2.70 *d*	1.87–1.92 *m*	—
				2.34 *m*
11	2.60 –	1.85–2.05 *m**	1.74 *br ddd*	2.19 *m*
12	2.45 *m*	2.52–2.68 *m**	2.58–2.44 *m*	2.51 *br t*
14	6.30 *br s*	6.26 *br s*	6.28 *br s*	6.31 *br s*
15	7.36 *dd*	7.33 *dd*	7.36 *dd*	7.37 *dd*
16	7.26 *br s*	7.21 *br s*	7.24 *br s*	7.26 *br s*
17	1.84 *s*	1.05 *t*	1.28 *d*	1.86 *br s*
18	1.09 *s*	0.75 *s*	0.85 *s*	0.83 *s*
19	1.31 *s*	1.03 *s*	1.24 *s*	1.23 *s*
20	1.42 *s*	1.03 *s*	0.84 *s*	0.91 *s*
OH	3.32 *d*	3.01 *s*		

*Not of first order.

J (Hz): Compound **3**: 1α,1β = 1α,2β = 2α,2β = 2β,3α = 3α,3β = 13; 1α,2α = 2α,3α = 4; 1β,2α = 1β,2β = 2α,2β = 2β,3β = 3; 5,6 = 3.5; 6,OH = 3; 14,15 = 15,16 = 1.5.

Compound **4**: 5,6 = 11.5; 8,17 = 7.

Compound **5**: A/2α.3α = 4.5; 2β,3α = 3α,3β = 13; 5,7 = 1; 7,8 = 11.5; 8,17 = 6.5; 11,11′ = 14; 11,12 = 5; 11,12′ = 9; 14,15 = 15,16 = 1.5. B/2α,3α = 4; 2α,3β = 2β,3β = 3; 2β,3α = 3α,3β = 13; 11,12 = 11′,12 = 8; 14,15 = 15,16 = 1.5.

experiment. The ^{13}C NMR data are listed in Table 3. The most important correlation was observed between H-7 of the subunit (A) and C-7 of the subunit (B). The stereochemistry was deduced from the results of NOE difference spectroscopy, which are listed in the Table 3. The diaxial orientation of H-7 and H-8 (subunit A) was already indicated by the coupling $J_{7,8} = 11.5$ Hz and further supported by NOE effects between H-7_A and H-5_A as well as between H-20_A and H-8_A. More problematic was the stereochemistry at C-7 of the subunit (B). A weak NOE effect between H-20_B and 7_B indicated a 7α-oxygen function. The final confirmation was achieved after $LiAlH_4$ reduction and formation of two isomers. The couplings in the ring B of the subunit (A) indicated the same stereochemistry in both isomers with a 6β-hydroxy group, obviously formed by hydride attack from the less hindered α-side. In the subunit (B) of the main product, the couplings indicated a 6β-hydroxy group while in the minor compound the large coupling $J_{5,6} = 12$ Hz indicated a 6α-hydroxy group. On the other hand, in both compounds the coupling $J_{6,7}$ in the subunit (B) was small, indicating the axial orientation of the substituent at C-7_B. The stereochemistry was confirmed by the NOE results (Table 4). In particular, the strong effects of both axial methyl groups (C-19 and C-20) and H-6 in **5b** are important. The compounds were formed in the ratio 3:1.

The ^{1}H NMR data are listed in Table 5 and the ^{13}C NMR data for the main product in Table 2. The chemical shifts of H-7 in the natural compound and both reduction products, in particular those of the subunit (B), are worthy of note. Usually, an allylic proton in an α-position to a keto group on an oxygen-bearing carbon is shifted more downfield. The shielding cone of the carbonyl group in the counterpart could be responsible for the upfield shift in the natural compound. In the reduction product, the α-effect is missing causing an upfield shift, but the shielding effect of the counterpart is no longer present. The strong NOE effect between certain signals of the different subunits (Table 3) indicated a preferred conformation. Similar effects were observed in the spectra of the reduction products (Table 4). The conformational behaviour and synthesis of model compounds are presently under investigation. We have named compound **5** persianone.

EXPERIMENTAL

The air-dried aerial parts (1350 g) were collected in July 1992 in Eghleed, Province Farss, Iran (voucher 90/125, deposited in the Herbarium of the Dept. of Botany, Shahid Beheshty University, Eveen, Tehran, Iran) and extracted with petrol–Et_2O–MeOH (1:1:1).

Table 2. ^{13}C NMR data of compounds **2**–**5** (100 MHz, CDCl$_3$)

				5		
C	**2***	**3**	**4**	A	B	Multiplicity
1	31.6	37.4	31.8	31.5	36.5	*t*
2	18.1	18.6	19.3	18.2	18.7	*t*
3	42.0	43.2	41.3	42.3	42.2	*t*
4	32.2	33.9	32.3	32.3	32.1	*s*
5	55.9	53.2	55.6	57.4	58.3	*d*
6	212.0 *s*	70.7 *d*	81.8 *d*	210.7 *s*	211.3 *s*	
7	77.1 *d*	199.4 *s*	214.8 *s*	65.0 *d*	67.9 *d*	
8	47.6 *d*	128.2 *s*	32.4 *t*	50.5 *d*	128.1 *s*	
9	77.2	169.8	108.0	77.0	144.4	*s*
10	49.0	41.1	48.9	48.7	45.1	*s*
11	34.2	30.6	36.0	34.6	29.2	*t*
12	21.2	24.2	18.7	21.5	25.4	*t*
13	124.7	124.3	124.8	124.9	125.1	*s*
14	110.6	110.4	110.8	110.7	110.7	*d*
15	143.2	142.9	142.8	143.0	142.8	*d*
16	138.6	138.5	138.6	138.6	138.5	*d*
17	12.4	11.6	7.5	13.1	16.5	*q*
18	32.6	32.4	33.8	32.7	33.1	*q*
19	22.2	23.9	22.0	22.3	21.9	*q*
20	18.0	18.6	16.8	18.0	21.3	*q*

Assigned with aid of 2D-hetero COSY.

*Data taken from the lit. [1]; assignments corrected based on 2D-hetero COSY.

^{13}C NMR data of compound **5a**

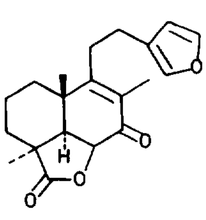
C	A	B	C	A	B
1	34.3 *t*	39.6 *t*	11	35.3 *t*	28.9 *t*
2	18.7 *t*	19.2 *t*	12	22.7 *t*	25.2 *t*
3	43.5 *t*	42.8 *t*	13	125.2 *s*	125.2 *s*
4	33.7 *s*	34.3 *s*	14	110.8 *d*	110.8 *d*
5	47.4 *d*	48.6 *d*	15	143.0 *d*	142.8 *d*
6	67.0 *d*	71.6 *d*	16	138.5 *d*	138.5 *d*
7	65.1 *d*	67.6 *d*	17	12.4 *q*	18.9 *q*
8	36.4 *d*	124.4 *s*	18	33.9 *q*	33.9 *q*
9	78.4 *s*	144.7 *s*	19	24.6 *q*	24.1 *q*
10	42.8 *s*	39.1 *s*	20	19.8 *q*	21.5 *q*

Assigned with aid of HMQC experiment.

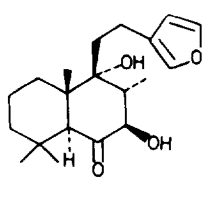
Table 3. NOE results and long range correlation of compound **5**

H	NOE H*	HMBC C*
5_A	7 (6%); 1α (2%); 3α (4%); 18 (3%)	4, 6, 10, 19, 20
5_B	1α (3%); 3α (3%); 18 (3%)	4, 6, 10, 19, 20
7_A	5 (3%); 7_B (2.5%); 17 (2%)	6, 8, 17, 7_B
7_B	7_A (5%); 17 (3%); 14_A (5%)	6, 8, 9
17_A	7 (2%); 7_B (5%); 17_B (3%); 12′ (3%)	6, 8, 9
17_B	Overlapped with H-8_A and H-12_A—no selectivity	7, 8, 9
18_A	5 (7%); 19 (5%); 3α (4%); 3β (5%)	7, 8, 9
18_B	5 (7%); 7_A (1%); 19 (5%); 3α (5%); 3β (5%)	3, 4, 5, 19
$19_A(3\beta_A)$	2β; 18 (3%); 20 (7%)	3, 4, 5, 19
$19_B(3\beta_A)$	2β; 18 (3%); 20 (7%)	3, 4, 18
20_A	2β; 11; 12; 8 (8%); 19 (7%)	1, 5, 9, 10
20_B	2β; 11′; 1β; 7 (1.5%); 19 (6%)	1, 5, 9, 10

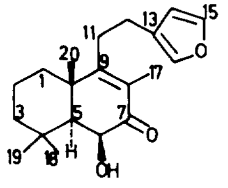
*Numbers without indices within the same subunit.



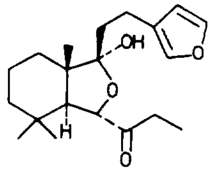
1



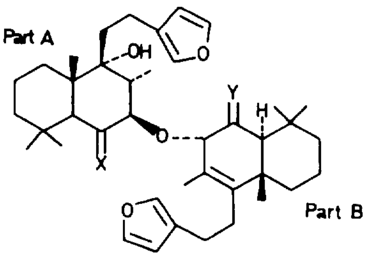
2



3



4



	5	5a	5b
X	O	βOH, H	βOH, H
Y	O	βOH, H	αOH, H

The extract was suspended in hot MeOH (10 ml g^{-1} of extract) and then cooled to $-15°$. After standing for 5 hr at $-15°$, the waxy ppt. was removed by filtration, and the filtrate evapd *in vacuo*. This yielded a green, dense oil, which was then fractionated by CC on silica gel. The fractions obtained with Et_2O–petrol (2:3) were separated by prep. TLC (silica gel, HF 254) affording 28 mg **5** [TLC: Et_2O–petrol (1:1), R_f 0.6], 15 mg **4** and 20 mg **3** [HPLC: R_p 8, MeOH–H_2O (9:1), Ca 100 bar, flow rate 3 ml min^{-1}, R_t 5.5 and 7.5 min, respectively].

6β-Hydroxy-15,16-epoxy-labda-8,13(16),14-trien-7-one (**3**). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 1680, 880; MS *m/z* (rel. int.):

Table 4. Selected NOEs with compounds **5a** and **5b**

H	Compound **5a**
5_A	6 (5%), 7 (5%), 18 (3%)
6_A	6_B (4%), 7 (5%), 7_B (3%), 18 (5%)
7_A	6 (4%), 6_B (1.5%), 7_B (4%)
18_A	5 (7%), 6 (7%), 19 (4%)
19_A	No selectivity
20_A	No selectivity
5_B	6 (5%), 18 (3%)
6_B	5 (5%), 6_A (3%), 7_A (1%), 18 (5%)
7_B	6_A (3%), 6 (4%), 7_A (4%), 17 (4%)
18_B	5 (7%), 6 (8%), 19 (4%)
19_B	No selectivity
20_B	No selectivity
	Compound **5b**
18_A	5 (7%), 6 (7%), 19 (4%)
19_A	No selectivity
20_A	No selectivity
18_B	5 (7%), 19 (4%)
19_B	6 (4%), 18 (4%), 20 (3%)
20_B	6 (8%), 19 (3%)

Table 5. Selected ^1H NMR data of reduction products **5a** and **5b** ($CDCl_3$, 400 MHz)*

	5a		**5b**	
H	A	B	A	B
5	1.50 *d*	1.47 *br s*	1.46 *d*	1.31 *d*
6	4.00 *dd*	4.13 *br s*	4.17 *br s*	3.93 *br dd*
7	2.69 *dd*	2.78 *br d*	2.96 *br dd*	2.97 *br d*
8	1.92 *m*	—	2.01 *m*	—
14	6.27 *br s*	6.31 *br s*	6.27 *br s*	7.36 *br s*
15	7.36 *dd*	7.37 *dd*	7.36 *br s*	7.36 *br s*
16	7.25 *br s*	7.22 *br s*	7.24 *br s*	7.23 *br s*
17	1.16 *d*	1.86 *br s*	1.16 *d*	1.81 *br s*
18	1.01 *s*	1.05 *s*	1.02 *s*	1.21 *s*
19	1.27 *s*	1.21 *s*	1.26 *s*	1.11 *s*
20	1.26 *s*	1.32 *s*	1.27 *s*	1.04 *s*

J (Hz): 14,15 = 15,16 = 1.5.
Compound **5a**: A/5,6 = 2; 6,7 = 3.5; 7,8 = 11; 8,17 = 7.
B/6,7 = 2.
Compound **5b**: A/5,6 = 1.5; 6,7 = 3.5; 7,8 = 11; 8,17 = 7.
B/5,6 = 11.5; 6,7 = 4.
*The signals for H-1 to H-3 overlapping multiplets.

316.214 $[M]^+$ (35) (calc. for $C_{20}H_{28}O_3$: 316.214), 235 $[M - C_5H_5O]^+$ (15), 211 (42), 193 (88), 181 (82), 81 (100), 65 (86); $[\alpha]^{24^\circ}$ −34 ($CHCl_3$; *c* 0.65).

seco-Labdane (**4**). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 1710, 880; MS *m/z* (rel. int.): 334.214 $[M]^+$ (16) (calc. for $C_{20}H_{30}O_4$: 334.214), 316 $[M - H_2O]^+$ (18), 235 (12), 95 (60), 82 (100), 81 (83), 69 (72).

Persianone (**5**). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 1710, 1680, 880; MS *m/z* (rel. int.): 632.407 $[M]^+$ (62) (calc. for $C_{40}H_{56}O_6$: 632.407), 616 (64), 551 (40), 550 (65), 536 (44), 356 (55), 354 (57), 315 (62), 314 (100), 95 (75), 81 (92); $[\alpha]^{24^\circ}$ −24 ($CHCl_3$; *c* 0.85).

Compound **5** (10 mg) in 1 ml Et_2O were stirred with excess of $LiAlH_4$ at room temp. for 5 hr. After usual work up and TLC (EtOAc–petrol, 1:1), 1 mg **5b**, 3 mg **5a** and 2 mg starting material were obtained. **5a**: MS *m/z*: 636 $[M]^+$ (6), 618 $[M - H_2O]^+$ (8), 600 $[618 - H_2O]^+$ (3), 335 (30), 318 (40), 310 (80), 300 (60), 95 (85), 81 (100).

REFERENCES

1. Rustaiyan, A., Mosslemin-Kupaii, M. H. and Zdero, C. (1992) *Phytochemistry* **31**, 334.
2. Savona, G., Piozzi, F., Hanson, J. R. and Siverns, M. (1977) *J. Chem. Soc., Perkin Trans. I* 322.
3. Savona, G., Piozzi, F., Hanson, J. R. and Siverns, M. (1976) *J. Chem. Soc., Perkin Trans. I* 1607.
4. Savona, G., Piozzi, F., Hanson, J. R. and Siverns, M. (1977) *J. Chem. Soc., Perkin Trans. I* 497.
5. Savona, G., Bruno, M., Piozzi, F. and Barbagallo, C. (1982) *Phytochemistry* **21**, 2132.