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S. Milosavljevi#, S. Macura, M. Stefanovi#, I. Aljan#i#, and D. Milinkovi#

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SESQUITERPENE LACTONES FROM *ACHILLEA CRITHMIFOLIA*<sup>1</sup>

S. MILOSAVLJEVIĆ,\* S. MACURA, M. STEFANOVIĆ,

Faculties of Chemistry and Physical Chemistry, University of Belgrade, Studentski trg 16,  
P.O. Box 550, YU-11001 Belgrade, Yugoslavia

I. ALJANČIĆ,

Institute for Chemistry, Technology and Metallurgy, Njegoševa 12, YU-11000 Belgrade, Yugoslavia

and D. MILINKOVIĆ

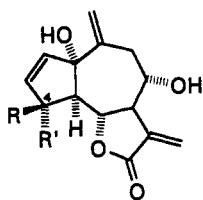
Institute for Pharmacognosy, Faculty of Pharmacy, Vojvode Stepe 450, YU-11000 Belgrade, Yugoslavia

ABSTRACT.—The isolation of three highly oxygenated guaianolides, desacetyl-1 $\alpha$ ,4 $\alpha$ -dihydroxybishopsolicepolide **1**, its 4 $\beta$ -hydroxy epimer **2** (a new compound), and 1 $\beta$ ,2 $\beta$ :3 $\beta$ ,4 $\beta$ -diepoxy-8 $\alpha$ ,10 $\alpha$ -dihydroxyguaia-11(13)-en-12,6 $\alpha$ -olide **3**, from the aerial parts of *Achillea crithmifolia* is reported. Because lactone **3** was shown to be identical with rupin A, the initially proposed 1 $\alpha$ ,2 $\alpha$ :3 $\alpha$ ,4 $\alpha$ -diepoxy stereochemistry of rupin A should be revised.

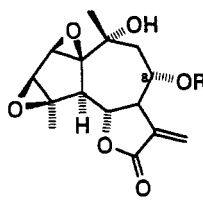
Four guaianolides (rupicolins A and B and their acetates) and a new germacranolide, 1 $\beta$ ,10 $\alpha$ -epoxy-3 $\beta$ ,9 $\beta$ -diacetoxy-11 $\alpha$ ,13-dihydrocostunolide, were previously isolated from the aerial parts of *Achillea crithmifolia* Waldst. et Kit. (Asteraceae), collected in summer 1988 at Rtanj mountain (Eastern Serbia) (1). The known flavonoid jaceidin was also isolated from the same extract. This time we investigated the aerial parts of the same species, originating from the vicinity of Donji Milanovac (Eastern Serbia). Instead of the CHCl<sub>3</sub> extraction followed by treatment with aqueous lead diacetate used in the previous study, the standard procedure currently employed in similar investigations (i.e., extraction with petroleum ether/Et<sub>2</sub>O/MeOH) (2) was applied.

## RESULTS AND DISCUSSION

Si gel cc of the extract yielded five  $\gamma$ -lactones, all exhibiting an  $\Delta^{11,13}$  double bond. By analogy of their spectral data to those reported, three were assigned as desacetyl-1 $\alpha$ ,4 $\alpha$ -dihydroxybishop-solicepolide **1** (3) (see <sup>1</sup>H-nmr data measured in CDCl<sub>3</sub>/CD<sub>3</sub>OD, Table 1), ridentin (4), and ridentin B (4). The co-occurrence of ridentin and ridentin B is quite usual (4). The similarity of <sup>1</sup>H-nmr data of lactone **2** to those of the known lactone **1** (Table 1) indicated an epimeric relationship between these compounds. This was partly proved by the Phase Sensitive NOESY (measured in C<sub>5</sub>D<sub>5</sub>N), which revealed the interproton dipolar coupling network in both lactones. The nOe's observed in these experiments enabled stereochemical assignment of **2** (with exception of configuration at C-1) and confirmation of the stereochemistry previously proposed for **1** (3). The nOe's H-5/H-7 and H-6/H-8 observed in phase-sensitive NOESY of both compounds



**1** R=Me, R'=OH  
**2** R=OH, R'=Me



**3** R=H  
**4** R=Ac

<sup>1</sup>Part II. For Part I see Milosavljević *et al.* (1).

TABLE 1. <sup>1</sup>H-nmr Data of Compounds **1** and **2**.

Proton	Compound			
	1 <sup>a</sup>	1 <sup>b</sup>	2 <sup>a</sup>	2 <sup>b</sup>
H-2 . . . . .	5.85 d (5.6)	5.59 [5.54]	5.96 d (5.6)	5.69
H-3 . . . . .	6.21 d (5.6)	5.90 [5.85]	6.16 d (5.6)	5.90
H-5 . . . . .	3.24 d (11.4)	2.38 [2.33]	2.70 d (10.7)	2.17
H-6 . . . . .	4.48 dd (11.4, 8.4)	4.11 [4.06]	4.36 dd (10.7, 8.4)	4.28
H-7 . . . . .	4.04 dddd (10.0, 8.4, 3.1, 3.4)	3.41 [3.35]	4.02 dddd (10.0, 8.4, 3.1, 3.4)	3.34
H-8 . . . . .	4.16 dt (6.0, 10.0)	3.71 [3.66]	4.15 m	3.74
H-9 $\alpha$ . . . . .	3.78 dd (13.0, 10.0)	2.95 [2.90]	3.77 dd (13.0, 9.0)	2.92
H-9 $\beta$ . . . . .	2.98 dd (13.0, 6.0)	2.58 [2.53]	2.96 dd (13.0, 6.0)	2.59
H-13 . . . . .	6.56 dd (3.4, 2.1)	6.32 [6.26]	6.56 t (3.1)	6.33
	6.81 dd (3.1, 2.1)	6.40 [6.33]	6.84 t (3.4)	6.41
H-14 . . . . .	4.97 d (1.8)	4.80 [4.77]	5.19 s	5.00
	5.10 s (br)	5.04 (5.00)	5.30 d (1.6)	5.10
H-15 . . . . .	1.62 s	1.31 [1.27]	1.76 s	1.57

<sup>a</sup>Chemical shifts,  $\delta$ , multiplicity (couplings, Hz) measured in C<sub>5</sub>D<sub>5</sub>N+TMS at 500 MHz, assigned by means of characteristic chemical shifts, coupling patterns and 2D nmr techniques, such as Phase Sensitive Double Quantum Filtered COSY and Phase Sensitive NOESY.

<sup>b</sup>Chemical shifts,  $\delta$ , measured in CDCl<sub>3</sub>/CD<sub>3</sub>OD (4:1)+TMS at 500 MHz; literature (3) data [400 MHz, CDCl<sub>3</sub>-CD<sub>3</sub>OD (4:1)] of desacetyl-1 $\alpha$ ,4 $\alpha$ -dihydroxybishopsolicepolide given in square brackets (multiplicity corresponded to that of previous column).

were in accordance with the same geometry for the C-5-C-6-C-7-C-8 fragment in **1** and **2**.

Although the nOe experiments did not provide any information for the configuration at C-1, the close similarity (between **1** and **2**) of <sup>1</sup>H nmr data for the C-9 methylene (in both solvents), which should sense anisotropic effects of groups at  $\gamma$ -positioned C-1 (5), were in accordance with the same relative configuration at C-1 [i.e., 1 $\alpha$ -OH, according to the previous proposal for **1** (3)] in these lactones. The biggest differences between the NOESY data of **1** and **2** were those concerning protons of the methyl group, i.e., H-15/H-5 and H-15/H-6. Whereas in **1** (according to the relative intensity of the corresponding cross peak in the NOESY) the nOe between H-15 and  $\beta$ -oriented H-6 was relatively intense, in compound **2** this nOe was very weak. At the same time, the nOe between H-15 and the  $\alpha$ -oriented H-5 was much more intense in **2**. These data clearly indicated 4 $\alpha$ -Me (4 $\beta$ -OH) orientation in **2** and, as previously proposed (3), 4 $\beta$ -Me (4 $\alpha$ -OH) geometry in **1**. This was also in accordance with the observed upfield shift of H-5 ( $\Delta\delta = -0.21$  ppm) and downfield shift of H-6 ( $\Delta\delta = 0.17$  ppm) of **2** (in CDCl<sub>3</sub>/CD<sub>3</sub>OD), in comparison to that of **1**. The analogous effects caused by different geometry at C-4 in the related compounds were previously reported (3). The reverse situation observed in C<sub>5</sub>D<sub>5</sub>N (i.e., upfield shift of H-6 in **2**) could be explained by the anisotropic influence of aromatic solvent.

Diepoxylactone **3** exhibited <sup>1</sup>H-(C<sub>5</sub>D<sub>5</sub>N) nmr data (Table 2) very similar to those reported (6,7) for a guaianolide known as rupin A to which the 1 $\alpha$ ,2 $\alpha$ :3 $\alpha$ ,4 $\alpha$ -diepoxy configuration was assigned (6), which indicated that those two were the same compound. In order to gain more evidence regarding this proposal, lactone **3** was converted to the corresponding 8-acetate **4**. The similarity of the <sup>1</sup>H-nmr spectrum (in C<sub>5</sub>D<sub>5</sub>N) of **4** to that of rupin B (7) (Table 2) was in accordance with the above conclusion. At the same time, <sup>1</sup>H-nmr data of **4** (in CDCl<sub>3</sub>) (Table 2) were almost identical to those reported (8) for yomogiartemin, i.e., 1 $\beta$ ,2 $\beta$ :3 $\beta$ ,4 $\beta$ -diepoxy analogue of rupin B. This could only mean that acetate **4**, rupin B, and yomogiartemin were the same compound, exhibiting

TABLE 2. <sup>1</sup>H-nmr Data of Compounds **3** and **4**.

Proton	Compound			
	<b>3</b> <sup>a</sup>		<b>4</b> <sup>b</sup>	<b>4</b> <sup>c</sup>
H-2	3.24 d (1.2)	[3.22]	3.24 [3.22]	3.24 [3.28]
H-3	3.78 d (1.2)	[3.75]	3.78 [3.73]	3.65 [3.68]
H-5	3.27 d (10.9)	[3.20]	3.26 [3.18]	2.83 [2.87]
H-6	4.59 dd (10.0, 10.9)	[4.52]	4.64 [4.56]	4.22 [4.27]
H-7	4.05 dddd (10.0, 9.2, 3.3, 3.6)	[4.13]	4.25 [4.13]	3.70 [3.74]
H-8	4.39 ddd (9.2, 6.6, 4.0)	[ca. 4.3]	5.54 [5.46]	5.24 [5.27]
H-9 $\alpha$	2.30 dd (15.5, 6.6)	[2.20]	2.06 [1.98]	1.55 [1.58]
H-9 $\beta$	2.56 dd (15.5, 4.0)	[2.55]	2.60 [2.57]	2.40 [2.40]
H-13	6.42 dd (3.6, 1.6)	[6.35]	5.68 [5.65]	5.53 [5.57]
	6.48 dd (3.3, 1.6)	[6.4]	6.28 [6.23]	6.20 [6.23]
H-14	1.25 s	[1.25]	1.23 [1.20]	1.09 [1.02]
H-15	1.52 s	[1.50]	1.51 [1.48]	1.55 [1.58]
OAc	—	—	2.00 [1.97]	2.11 [2.12]

<sup>a</sup>Chemical shifts,  $\delta$ , multiplicity (couplings, Hz) measured in C<sub>5</sub>D<sub>5</sub>N+TMS at 500 MHz, assigned by means of characteristic chemical shifts, coupling patterns and 2D nmr techniques (PS NOESY and PS DQF COSY); literature data (60 MHz, C<sub>5</sub>D<sub>5</sub>N) of rupin A (7) given in square brackets.

<sup>b</sup>Chemical shifts,  $\delta$ , measured under the same conditions as for **3**; literature data (60 MHz, C<sub>5</sub>D<sub>5</sub>N) of rupin B (7) given in square brackets.

<sup>c</sup>Chemical shifts,  $\delta$ , measured in CDCl<sub>3</sub>+TMS at 500 MHz; literature data (100 MHz, CDCl<sub>3</sub>) of yomogiartermine (8), given in square brackets.

the stereochemistry proposed for yomogiartermine since it was based on more reliable X-ray evidence (8), than that concerning rupin A and B (6). In favor of this geometry was also the similarity of the chemical shift of H-5 of **4** ( $\delta$  2.84 in DMSO-*d*<sub>6</sub>) to that of the same proton ( $\delta$  2.87, in DMSO-*d*<sub>6</sub>) of artecanin, desacetoxy analogue of **4**, with 1 $\beta$ ,2 $\beta$ :3 $\beta$ ,4 $\beta$ -diepoxy configuration (9). The erroneous configurations presented earlier (9) for canin and artecanin were subsequently revised (10,11). In addition, the initially proposed 10,1:2,3-diepoxyguaianolide structures for chrysartemins A and B (12) were revised to those of canin (10) and artecanin (11), respectively. In canin, the 1 $\alpha$ ,2 $\alpha$ :3 $\alpha$ ,4 $\alpha$ -diepoxy diastereomer of artecanin, the chemical shift of H-5 (also in DMSO-*d*<sub>6</sub>) was lower ( $\delta$  2.35) (9). A similar relationship between the chemical shift of H-5 of canin [ $\delta$  2.77 (7)] and that of the same proton of **3** and **4** ( $\delta$  3.27 and 3.26, respectively) [or rupin A and rupin B (7)] (see Table 2) was also observed in C<sub>5</sub>D<sub>5</sub>N.

## EXPERIMENTAL

**GENERAL EXPERIMENTAL PROCEDURES.**—Melting points were determined using a Boetius PHMK apparatus and are uncorrected. 1D and 2D nmr spectra were measured on a WM 500 Bruker spectrometer. Ci mass spectra were run on a Finnigan MAT 8230 double-focusing mass spectrometer. Ir spectra were recorded on a Perkin Elmer FT IR 1725X spectrometer. Optical rotations were taken on a Polamat A polarimeter, using 1 cm cell.

**MATERIAL.**—The plant *A. crithmifolia* (voucher specimen No. 120790 deposited at the Institute for Pharmacognosy, Belgrade) was collected in the summer of 1990 in the vicinity of Donji Milanovac (Serbia).

**ISOLATION PROCEDURE.**—A crude extract (140 g) obtained from the powdered air-dried aerial parts (3 kg), using extraction with petroleum ether-Et<sub>2</sub>O-MeOH (1:1:1) (2 $\times$ 6 liters), was chromatographed on a Si gel column. Elution began with petroleum ether followed by toluene, and the polarity of the solvent was gradually increased by addition of EtOAc. The fraction (4.5 g), eluted with EtOAc-toluene (7:3), was rechromatographed on a Si gel column (eluting with CHCl<sub>3</sub>/Me<sub>2</sub>CO, gradually increasing the percentage of Me<sub>2</sub>CO) and afforded five  $\gamma$ -lactones that eluted in the following order: **3** (8:2), **2** (7:3), ridentin + ridentin B, **1** (6:4) (the ratio of the CHCl<sub>3</sub>/Me<sub>2</sub>CO is given in parentheses).

*Desacetyl-1 $\alpha$ ,4 $\alpha$ -dihydroxybisbopsolicepolide* [1].—Identification based on the identity of its spectral data to published spectra (3). Yield 35 mg;  $^1\text{H}$  (500 MHz) nmr see Table 1;  $^{13}\text{C}$  (125 MHz) nmr ( $\text{C}_6\text{D}_6\text{N} + \text{TMS}$ ) (assigned by means of HETCOR)  $\delta$  85.5 (C-1 or C-4), 135.1 (C-2), 139.1 (C-3), 82.0 (C-1 or C-4), 67.2 (C-5), 79.4 (C-6), 49.2 (C-7), 73.8 (C-8), 42.7 (C-9), 148.1 (C-10), 141.5 (C-11), 171.1 (C-12), 124.4 (C-13), 114.5 (C-14), 24.8 (C-15).

*Desacetyl-1 $\alpha$ ,4 $\beta$ -dihydroxybisbopsolicepolide* [2].—Yield 17 mg;  $\text{C}_{15}\text{H}_{18}\text{O}_5$ ; amorphous white solid;  $[\alpha]_D^{25} + 121.1$  ( $c=0.83$ , MeOH); cims  $m/z$   $[\text{M} + 1]^+$  279; ir (film) 3432, 1749, 1647  $\text{cm}^{-1}$ ;  $^1\text{H}$  (500 MHz) nmr see Table 1;  $^{13}\text{C}$  (125 MHz) nmr ( $\text{C}_6\text{D}_6\text{N} + \text{TMS}$ ) (assigned by comparison with the spectrum of compound 1)  $\delta$  86.6 (C-1 or C-4), 135.3 (C-2), 138.0 (C-3), 81.6 (C-1 or C-4), 64.5 (C-5), 79.1 (C-6), 49.6 (C-7), 74.0 (C-8), 42.7 (C-9), 149.7 (C-10), 139.8 (C-11), 171.1 (C-12), 124.1 (C-13), 115.8 (C-14), 30.0 (C-15).

*1 $\beta$ ,2 $\beta$ :3 $\beta$ ,4 $\beta$ -Diepoxy-8,10 $\alpha$ -dihydroxyguai-11(13)*en*-12,6 $\alpha$ -olide (rupin A)* [3].—Yield 5 mg;  $\text{C}_{15}\text{H}_{18}\text{O}_6$ ; mp (dec) 285–350°;  $[\alpha]_D^{25} + 29.35$  ( $c=0.31$ ,  $\text{C}_6\text{H}_6\text{N}$ ); cims  $m/z$   $[\text{M} + 1]^+$  295; ir (film) 3488, 3466, 1742, 1699  $\text{cm}^{-1}$ ;  $^1\text{H}$  (500 MHz) nmr ( $\text{C}_6\text{D}_6\text{N} + \text{TMS}$ ) was in agreement with that of rupin A (see Table 2);  $^{13}\text{C}$  (125 MHz) nmr ( $\text{C}_6\text{D}_6\text{N} + \text{TMS}$ ) [partially assigned by characteristic chemical shifts  $\delta$  70.7, 70.5, 69.5, 58.3, 57.4 (C-1,-2,-3,-4,-8,-10; in the region two lines are overlapped)], 52.5 (C-5), 78.5 (C-6) 49.3 (C-7), 44.9 (C-9), 140.3 (C-11), 170.0 (C-12), 121.6 (C-13), 27.0 (C-14), 20.5 (C-15). Compound 3 was acetylated, using the standard procedure ( $\text{Ac}_2\text{O}/\text{C}_6\text{H}_6\text{N}$ ) to give 4, whose  $^1\text{H}$ -nmr data in Table 2 were in agreement with those of rupin B (7) and yomogiartemin (8).

Ridentin and ridentin B the coeluting compounds, were separated by preparative tlc [ $\text{C}_6\text{H}_6$ - $\text{Et}_2\text{O}$ -MeOH (18:1:1) after three developments] of the corresponding diacetates to which this mixture was converted by treatment with  $\text{Ac}_2\text{O}/\text{C}_6\text{H}_6\text{N}$ . Yields were 12 mg of ridentin diacetate and 10 mg of ridentin B diacetate. Compounds were identified by comparison of the  $^1\text{H}$ -nmr spectral data (not shown) to those published (4).

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