Chemistry of Natural Compounds, Bioorganic, and Biomolecular Chemistry

Migration of the *O*-acetyl group in the acetonation of guaianolide rhaposerin

A. G. Berdin,[a] V. A. Raldugin,[b]★ M. M. Shakirov,[b] A. G. Druganov,[b] I. Yu. Bagryanskaya,[b] Yu. V. Gatilov,[b] A. T. Kulyyasov,[a] S. M. Adekenov,[a] and G. A. Tolstikov[b]

[a]*Institute of Phytochemistry, Ministry of Education and Sciences of the Kazakhstan Republic, 4 ul. Gazalieva, 470032 Karaganda, Kazakhstan Republic. Fax: +7 (321 2) 43 3773. E-mail: arglabin@phyto.karaganda.su*

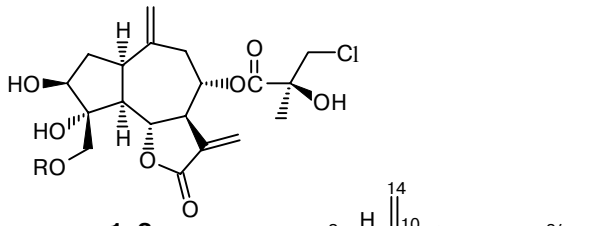
[b]*N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Akad. Lavrent'eva, 630090 Novosibirsk, Russian Federation. Fax: +7 (383 2) 35 4752. E-mail: raldugin@nioch.nsc.ru*

Acetonation of rhaposerin is accompanied by migration of the *O*-acetyl group. Acetonation of 15-*O*-deacetylrhaposerin afforded isomeric *O*-isopropylidene derivatives containing five- and six-membered rings.

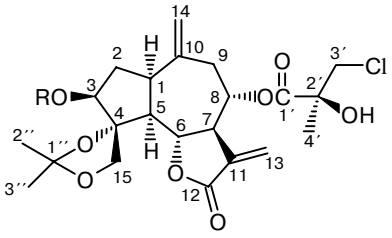
Key words: sesquiterpenoids, guaianolides, 15-*O*-deacetylrhaposerin, rhaposerin, acetonides, X-ray diffraction analysis, HPLC, 2D NMR spectroscopy.

The above-ground part of the herb *Rhaponticum serratuloides* (Georgi.) Bobr. is rich in sesquiterpene lactones, two of which, *viz.*, rhaposerin (**1**)[1] and 15-*O*-deacetylrhaposerin (**2**),[2] being rather accessible compounds similar in chemical composition. The structure of *O*-isopropylidene derivative **3** obtained from lactone **2** has been unambiguously established by X-ray diffraction analysis.

Acetonation of lactone **1**, which contains vicinal *trans*-hydroxy groups and cannot therefore form the 3,4-*O*-isopropylidene derivative, afforded crystalline compound **4** under the conditions described earlier.[2] Its structure was established by X-ray diffraction analysis (Fig. 1). The seven-membered rings of compounds **3** and **4** differ in the conformation of the C(8)—C(9)—C(10)=C(14)—C(1) fragment; the



1, **2**



3, **4**

R = COMe (**1**, **4**), H (**2**, **3**)

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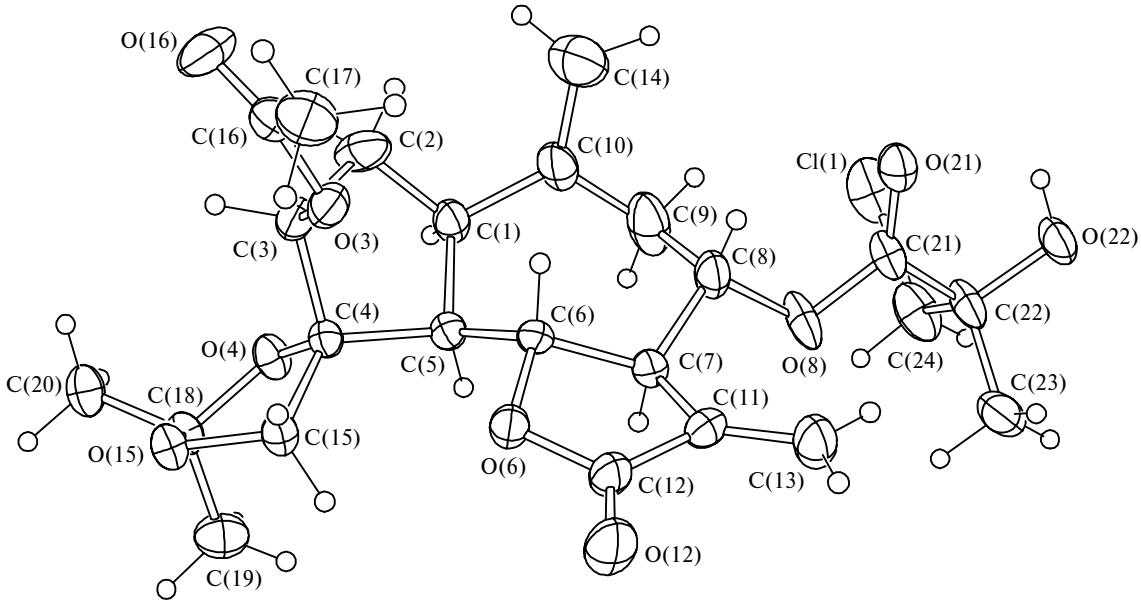
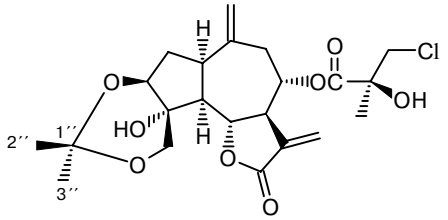


Fig. 1. Molecular structure of acetonide **4**.

C(8)—C(9)—C(10)—C(1) torsion angles are −89.3(7)° in molecule **4** and 85.7(5)° and 86.1(6)° in two crystallographically independent molecules of acetonide **3**.[2] The seven-membered ring of molecule **4** adopts a *twist*-chair conformation, like that in the molecule of the known guaianolide 8α-hydroxy-11α,13-dihydrozaluzanin C.[3]

Apparently, acetonide **4** was formed upon the O(C(15))→O(C(3)) migration of the acetyl group followed by the formation of the 4,15-*O*-isopropylidene group.

One would expect that acetonation of triol **2** will afford acetonide **5** (isomeric with compound **3**) containing the 1,3-dioxane ring, which is typical of carbohydrates.[4] Actually, isomer **5** was obtained in the reaction of lactone **2** with acetone in the presence of TsOH. Its structure was confirmed by the data from mass spectrometry and the ^{13}C and ^{1}H NMR spectra, which were interpreted (Tables 1 and 2, respectively) using 2D $^{1}H—^{1}H$ (COSY) and $^{13}C—^{1}H$ (COSY and COLOC) NMR spectroscopy.



5

Isomeric acetonides **3** and **5** were readily separated by reversed-phase HPLC; the capacity factors (k') for compound **3** in 50, 60, and 70% solutions of MeOH in 0.05 *M* aqueous H_3PO_4 as the eluent were 9.6, 2.7, and 1.1, respectively; the corresponding factors for acetonide **5** were 4.8, 1.6, and 0.72, respectively. The UV spectra of isomers **3** and **5**, which were measured in the stop-flow mode, are similar. They have a maximum at 196 nm and a shoulder at 216 nm.

As in other analogous cases,[4] the formation of acetonides **3** and **5** is apparently kinetically controlled. Acetonides **3** and **5** were obtained as an equilibrium

Table 1. ^{13}C NMR spectra of compounds **3**—**5**

C atom	δ		
	3[2]	**4**	**5**
C(1)	46.88 (d)	46.12 (d)	47.53 (d)
C(2)	38.73 (t)	35.83 (t)	37.91 (t)
C(3)	75.52 (d)	77.84 (d)	79.24 (d)
C(4)	93.20 (s)	91.51 (s)	78.86 (s)
C(5)	57.06 (d)	56.71 (s)	59.81 (d)
C(6)	77.17 (d)	76.23 (d)	77.60 (d)
C(7)	47.49 (d)	48.05 (d)	46.98 (d)
C(8)	75.49 (d)	75.27 (t)	75.12 (d)
C(9)	35.74 (t)	36.38 (t)	35.54 (t)
C(10)	143.82 (s)	142.38 (s)	169.29 (s)
C(11)	138.83 (s)	138.21 (s)	138.49 (s)
C(12)	169.19 (s)	168.99 (s)	173.44 (s)
C(13)	121.22 (t)	121.74 (t)	121.16 (t)
C(14)	117.66 (t)	118.64 (t)	117.43 (t)
C(15)	66.13 (t)	66.07 (t)	66.23 (t)
C(1′)	174.44 (s)	173.45 (s)	173.44 (t)
C(2′)	75.37 (s)	75.42 (s)	75.37 (s)
C(3′)	52.15 (t)	52.10 (t)	52.14 (t)
C(4′)	24.29 (q)	24.28 (q)	24.29 (q)
C(1″)	108.48 (s)	109.14 (s)	98.90 (s)
C(2″)	24.45 (q)	26.85 (q)	20.49 (q)
C(3″)	28.00 (q)	27.65 (q)	27.78 (q)
$CH_3\underline{C}O$	—	168.85 (s)	—
$\underline{C}H_3CO$	—	20.80 (q)	—

Table 2. ^{1}H NMR spectra of compounds **3**—**5**

Atom H	δ (*J*/Hz)		
	3	**4**	**5**
H(1)	3.48 (ddd, $J_{1,2\beta}$ = 11, $J_{1,2\alpha} = J_{1,5}$ = 8)	3.38 (ddd, $J_{1,2\alpha}$ = 11, $J_{1,2\beta} = J_{1,5}$ = 8)	3.70 (ddd, $J_{1,2\alpha}$ = 11, $J_{1,2\beta} = J_{1,5}$ = 8)
H(2α)	2.49 (m)	2.49 (m)	2.55 (m)
H(2β)	1.76 (ddd, ^2J = 14.5, $J_{2\beta,3}$ = 1.5)	1.65 (ddd, ^2J = 12, $J_{2\beta,3}$ = 2.5)	1.78 (ddd, ^2J = 9, $J_{2\beta,3}$ = 2)
H(3)	4.34 (br.d, J = 5)	5.21 (br.d, $J_{2\alpha,3}$ = 6.5)	4.32 (dd, $J_{2\alpha,3}$ = 6; 2)
H(5)	2.43 (ddd, J = 11, $J_{3,5}$ = 1)	2.42 (m)	2.65 (dd, $J_{5,6}$ = 11.5)
H(6)	5.15 (dd, $J_{6,7}$ = 10)	4.68 (dd, $J_{6,5}$ = 11, $J_{6,7}$ = 9)	5.06 (dd, $J_{6,7}$ = 9.5)
H(7)	3.13 (dddd, $J_{7,8} = J_{6,7}$ = 10, $J_{7,13A}$ = 3, $J_{7,13B}$ = 3.5)	3.12 (dddd, $J_{7,8}$ = 7.5, $J_{7,13A}$ = 3, $J_{7,13B}$ = 3.5)	3.19 (dddd, $J_{7,8}$ = 6.5; $J_{7,13A}$ = 3, $J_{7,13B}$ = 3.5)
H(8)	5.32 (ddd, $J_{8,9A}$ = 2, $J_{8,9B}$ = 5)	5.28 (ddd, $J_{8,9A}$ = 3, $J_{8,9B}$ = 5.5)	5.46 (ddd, $J_{8,9A}$ < 1.5, $J_{8,9B}$ = 5)
H(9A)	2.49 (m)	2.41 (dd, $J_{9A,9B}$ = 15)	2.55 (m)
H(9B)	2.83 (dd, $J_{9A,9B}$ = 15)	2.65 (dd)	2.82 (dd)
H(13A)	5.75 (d, J = 3.0)	5.73 (d, J = 3.0)	5.78 (d, J = 3.0)
H(13B)	6.16 (d, J = 3.5)	6.11 (d, J = 3.5)	6.15 (d, J = 3.5)
H(14A)	5.05 (d, ^2J = 2.0)	5.02 (br.s)	5.07 (d, ^2J = 1.5)
H(14B)	5.08 (d)		5.16 (d)
H(15A)	4.53 (d, ^2J = 11.0)	4.33 (d, ^2J = 11)	4.13 (d, ^2J = 12)
H(15B)	4.77 (d)	4.42 (d)	4.61 (d)
H(3′A)	3.97 (d, ^2J = 11.0)	3.91 (d, ^2J = 11.5)	4.00 (d, ^2J = 11)
H(3′B)	4.07 (d)	4.01 (d)	4.11 (d)
H(3H(4′)	1.67 (br.s)	1.62 (s)	1.70 (s)
C$\underline{H}_3$CO	—	1.86 (s)	—
3H(2″)	1.35 (s)	1.31 (s)	1.38 (s)
3H(3″)	1.44 (s)	1.38 (s)	1.42 (s)

mixture with isomer **3** predominating. Thus 2 min after the addition of TsOH to a solution of lactone **2** in acetone, the starting compound was completely consumed and acetonides **3** and **5** were present in a ratio of 2.5 : 1 (HPLC). After 18 h, this ratio became equal to 11 : 1 and then remained unchanged. Under analogous conditions, the same equilibrium mixture was obtained from individual acetonides **3** and **5**.

Acetonides **3** and **5** were not detected (HPLC) in a mixture of lactones isolated from the plant under study.

Experimental

The melting points were determined on a Boetius instrument. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer (500.13 MHz for ^{1}H; 125.76 MHz for ^{13}C) in Py-d_5 with the use of the standard Bruker software for recording the 2D COSY and COLOC spectra (9 Hz) with Me_4Si as the internal standard.

The high-resolution mass spectra (EI, 70 eV) were obtained on a Finnigan MAT 8200 instrument. The IR spectra (KBr pellets) were recorded on a Vector-22 instrument. The optical rotation was measured on a Polamat A polarimeter at 580 nm. Column chromatography was carried out on silica gel (KSK); the compound to sorbent ratio was ~1 : 20. Flash chromatography was carried out on silica gel Armsorbsil. The TLC analysis was performed on Silufol plates; spots were visualized by spraying with a 1% vanilline solution in H_2SO_4. Rhaposerin (**1**) was prepared as described previously.[1] Acetone containing 0.01% of H_2O (Fischer titration) was additionally dried with B_2O_3 according to a known procedure.[5]

HPLC was performed on a Milikhrom microcolumn liquid chromatograph[6] (64×2-mm column; LiChrosorb RP-18 (Merck) as the sorbent, 5 μm) at 30 °C. The eluent was prepared by mixing MeOH with 0.05 *M* aqueous H_3PO_4. The compounds were detected at 200 nm. The rate of elution was 100 μL min^{-1}. The concentrations of the samples were approximately 1.2 mg mL^{-1} in MeOH. The 1.4-μL portions of the solution were injected into the column.

3-*O*-Acetyl-15-*O*-deacetyl-4,15-*O*-isopropylidenerhaposerin (4). TsOH (15 mg, 0.087 mmol) was added to a solution of lactone **1** (360 mg, 0.78 mmol) in dry Me_2CO (15 mL). The reaction mixture was kept at 20 °C for 30 min, diluted with AcOEt (75 mL), and washed successively with a 5% aqueous solution of $NaHCO_3$ (2×30 mL) and water (2×30 mL). The organic layer was separated, dried with anhydrous Na_2SO_4, and filtered. The solvent was evaporated *in vacuo*. Flash chromatography of the residue was carried out on a column with SiO_2 (36 g). Acetonide **4** was isolated by elution with a light petroleum—EtOAc mixture (10 : 3) in a yield of 171 mg (44%), m.p. 180—182 °C (from an EtOAc—light petroleum mixture), $[\alpha]^{19}_{580}$ +71 (*c* 0.84, Me_2CO). IR, ν/cm^{-1}: 1772 (γ-lactone); 1743 (C=O); 1662, 1641, 1373, 1273, 1239, 1138, 1057, 1111, 965, 852. MS, *m/z* (I_{rel} (%)): 485 [M(^{37}Cl) − CH_3]$^+$ (37), 483 [M(^{35}Cl) − CH_3]$^+$ (100), 380 (16), 260 (29), 242 (59), 245 (38), 197 (17), 147 (37), 130 (32), 129 (13), 93 (23), 91 (17). Found: *m/z* 483.14362 [M(^{35}Cl) − CH_3]$^+$. $C_{23}H_{28}O_9Cl$. Calculated: *M* = 483.14217. The ^{13}C and ^{1}H NMR spectroscopic data are given in Tables 1 and 2, respectively.

X-ray diffraction analysis of acetonide **4** was carried out on a Syntex $P2_1$ diffractometer (Cu-Kα radiation, graphite monochromator, θ/2θ scanning technique) from a crystal of dimensions 0.8×0.7×0.6 mm^3. Crystals of **4** belong to the trigonal system, $a = b$ = 12.616(3) Å, c = 13.528(3) Å, γ = 120°,

V = 1864.7(8) Å^3, space group $P3_2$, $C_{24}H_{31}O_9Cl$, M = 498.94, Z = 3, d_{calc} = 1.333 g cm^{-3}, μ = 1.79 mm^{-1}. A total of 4500 independent reflections with $2\theta < 140°$ were measured. The absorption correction was applied using the semiempirical method based on the ψ-scanning data (transmission was 0.55—0.96). The structure was solved by the direct method using the SHELXS-97 program package and refined by the full-matrix least-squares method in the anisotropic-isotropic (for H atoms) approximation using the SHELXL-97 program package to wR_2 = 0.1508, S = 0.924 (R = 0.0561 for 3279 $F_0 > 4\sigma$). The absolute configuration of the structure is characterized by Flack's parameter equal to −0.04(3).

The coordinates and the equivalent thermal parameters of the non-hydrogen atoms of molecule **4** were deposited with the Cambridge Structural Database.

15-*O*-Deacetyl-3,15-*O*-isopropylidenerhaposerin (5). TsOH (1.5 mg) was added to a solution of lactone **2** (100 mg, 0.25 mmol) in dry Me_2CO (2 mL). The reaction mixture was stirred at 20 °C for 30 min, diluted with EtOAc (30 mL), and washed with a 5% aqueous solution of $NaHCO_3$ (2×10 mL). The organic phase was separated and dried with Na_2SO_4. The solution was concentrated to dryness *in vacuo*. Flash chromatography of the residue on SiO_2 (5 g) (light petroleum—EtOAc, 4 : 1) afforded compounds **3** and **5** in yields of 35 mg (32%)[2] and 10 mg (9%), respectively, m.p. 109—112 °C, $[\alpha]^{22}_{580}$ +60.1 (*c* 2.93, Me_2CO). IR, ν/cm^{-1}: 1767 (γ-lactone); 1758 (C=O); 1695, 1640 (C=C); 1278, 1219, 1158, 1111, 1078, 1009, 981, 863. MS, m/z (I_{rel} (%)): 443 [M(^{37}Cl) − CH_3]$^+$ (14), 441 [M(^{35}Cl) − CH_3]$^+$ (35), 368 (22), 321 (14), 261 (60), 260 (91), 243 (40), 242 (34), 225 (14), 215 (24), 216 (36), 214 (33), 203 (63), 175 (36), 149 (41), 93 (74), 59 (23), 57 (15), 43 (100). Found: m/z 441.13705 [M(^{35}Cl) − CH_3]$^+$. $C_{21}H_{26}O_8Cl$. Calculated: M = 441.13161. The ^{13}C and ^{1}H NMR spectroscopic data are given in Tables 1 and 2, respectively.

Interconversion of acetonides 3 and 5. ***A.*** A small crystal of TsOH (~0.5 mg) was added to a solution of acetonide **3** (3 mg) in dry Me_2CO (1 mL) at 20 °C. The gradual formation of acetonide **5** was followed by HPLC. After 18 h, the **3** : **5** ratio was 11 : 1; the solution also contained lactone **2** in trace amounts.

B. The experiment with acetonide **5** was carried out analogously. After 70 min, acetonide **3** was found to be the major component in the mixture of the isomers. After 18 h, the ratio of acetonides **3** and **5** reached 11 : 1. The ratio of the acetonides remained virtually unchanged upon the addition of water (10 μL) with the use of a pump of a Milikhrom chromatograph, but trace amounts of lactone **2** were detected after 1 h.

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