

## CHEMICAL TRANSFORMATIONS OF AJANOLIDE A

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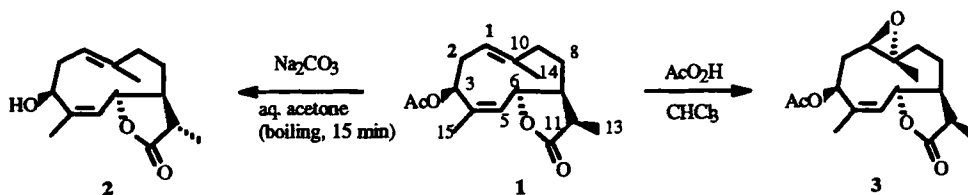
UDC 547.314:548.737

*The new sesquiterpene lactone ajanolide A has been subjected to hydrolysis and epoxidation. The structures of the derivatives obtained have been established by x-ray structural analysis.*

*E,Z*-Germacranolides (heliangolides) are frequently encountered in the plant world, as is shown by the increased number of reports of the isolation of compounds of this group from plant materials in recent years [1—3]. There are statements of a high antitumoral activity of the heliangolide hiyodorilactone A (1), isolated from *Eupatorium sachalinense* [4—6]

In the present paper we give the results of chemical transformations of the new sesquiterpene lactone ajanolide A (1), first isolated from *Ajania fruticulosa* (Ldb) Poljak [7].

When (1) was boiled with Na<sub>2</sub>CO<sub>3</sub> in aqueous acetone for 15 min, its deacetyl derivative (2), C<sub>15</sub>H<sub>22</sub>O<sub>3</sub>, was formed with a yield of 73%.



The IR spectrum of (2) contained absorption bands of an OH group in the 3606 and 3300—3600 cm<sup>-1</sup> regions and the absorption band of a  $\gamma$ -lactone C=O at 1769 cm<sup>-1</sup>. The action of peracetic acid on (1) led to the regio- and stereoselective formation of the 1 $\beta$ ,10 $\alpha$ -epoxy derivative (3) with the composition C<sub>17</sub>H<sub>24</sub>O<sub>5</sub> in a yield of 28%. The IR spectrum of (3) contained an absorption band in the 1780 cm<sup>-1</sup> region, characterizing the presence of a  $\gamma$ -lactone C=O, and absorption bands of an acetyl group at 1750, 1253, and 1210 cm<sup>-1</sup>. PMR spectra showed that the *cis*-C4=C5 double bond in the (1) molecule was not epoxidized. According to the literature, costunolide also forms a 1,10-epoxy derivative on interaction with per-acids [8].

Characteristic for the PMR spectra of compounds (1—3) was the evidence of a long-range SSCC (Table 1) with <sup>4</sup>J = 1.4—1.5 Hz between the H5 and CH<sub>3</sub>-15 protons. According to the literature, an analogous interaction with the same <sup>4</sup>J value is observed for the molecules of other germacranolides [9—11].

The signal of the H-3 proton in deacetyl ajanolide A (2) appeared in the form of a triplet with a SSCC of 3.4 Hz in the region of 4.45 ppm both in CDCl<sub>3</sub> and in Py-d<sub>5</sub> and was shifted upfield (by 0.43—0.71 ppm, depending on the solvent) in comparison with that for the initial lactone (1) and the epoxide (3). The PMR spectrum of (2) also lacked the signal of an acetyl group. The signal of the H-1 proton in epoxide (3) had a considerable upfield shift of 2.48 ppm in comparison with the H-1 signal of lactone (1).

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TABLE 1. Details of the PMR Spectra of Compounds (1—3)\*

Compound	H-1	H-3	H-5	H-6	H-11	H-13	H-14	H-15	OAc
<b>1</b> (C <sub>6</sub> D <sub>6</sub> , +60°C)	4.89 br.tr.(8.0)	5.10 dd (4.0, 2.5)	5.01 dq (11.0, 1.4)	5.07 dd (11.0, 1.6)	2.39 dq (10.0, 7.50)	1.02 d, (7.5)	1.65 br.s, 3H	1.59 d, (1.4)	1.77 s, 3H
<b>2</b> (CDCl <sub>3</sub> , +25°C, 200 MHz)	5.30 br.tr.(8.0)	4.45 tr.(3.3)	5.20 dq (10.0, 1.4)	5.65 dd (10.0, 7.0)	2.26 dq (9.0, 7.0)	1.26 d, (7.0)	1.56 br.s, 3H	.69 d, (1.4)	-
<b>2</b> Py=d <sub>5</sub> , +100°C, 500 MHz	5.35 br.tr.(8.0)	4.45 tr.(3.4)	5.16 dq (10.0, 1.4)	5.70 dd (10.0, 7.0)	2.16 dq (9.0, 7.0)	1.18 d, (7.0)	1.55 br.s, 3H	1.53 d, (1.4)	-
<b>3</b> (C <sub>6</sub> D <sub>6</sub> , +25°C, 400 MHz)	2.41 dd (10.0, 4.5)	4.88 dd (5.0, 2.2)	4.85 dq (11.5, 1.5)	5.29 dd (11.5, 1.0)	2.20 dq (9.0, 7.4)	0.91 d, (7.4)	1.22 s, 3H	1.55 d, (1.5)	1.77 s, 3H
<b>3</b> (CDCl <sub>3</sub> , +25°C, 500 MHz)	2.80 dd (10.0, 4.5)	5.16 dd (5.0, 2.2)	5.39 dq (11.5, 1.4)	5.50 d (11.5)	2.88 dq (9.0, 7.0)	1.15 d, (7.0)	1.41 s, 3H	1.87 d, (1.4)	2.07 s, 3H

\* SSCCs (Hz) are given in parentheses after the chemical shifts.

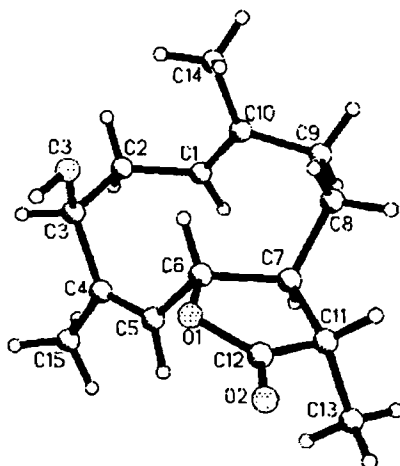


Fig. 1. Molecular structure of deacetylanolide A (2).

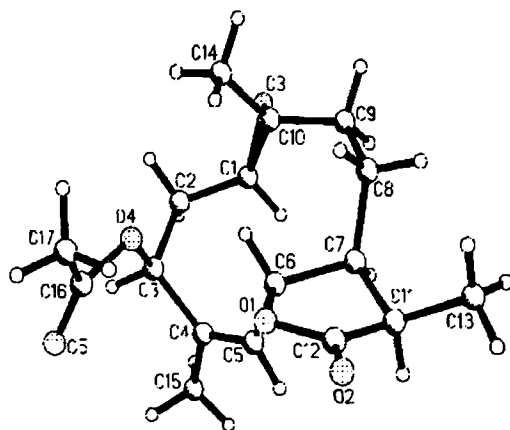


Fig. 2. Molecular structure of ajanolide 1 $\beta$ ,10 $\alpha$ -epoxide (3).

TABLE 2. Torsional Angles (degrees) in the Rings of Compounds (2) and (3)

Angle	2	3a	3b
Ring A			
C10C1C2C3	168.4	158.2	159.1
C1C2C3C4	-85.5	-87.9	-84.1
C2C3C4C5	-51.2	-45.0	-50.9
C3C4C5C6	88.1	83.3	80.8
C4C5C6C+	-2.1	-2.4	0.3
C5C6C7C8	-120.2	-128.2	-122.3
C6C7C8C9	134.7	141.3	146.2
C7C8C9C10	-82.5	-77.3	-83.2
C8C9C10C1	64.5	65.7	61.3
C9C10C1C2	-95.3	-91.2	-85.2
Ring B			
C6O1C12C11	2.0	-4.0	-0.1
O1C12C11C7	6.2	20.3	19.0
C12C11C7C6	-11.0	-27.0	-28.6
C11C7C6O1	12.1	25.4	28.8
C7C6O1C12	-9.2	-14.0	-18.8

Table 3. Coordinates of the Atoms of Structure (2) ( $\times 10^4$ ; for H,  $\times 10^3$ )

Atom	x	y	z
O1	3210(2)	4082(5)	498(2)
O2	3749(2)	5394(5)	-815(2)
O3	2398(2)	850(5)	2531(3)
C1	3214(3)	4113(9)	3995(3)
C2	2444(3)	2930(9)	4044(4)
C3	2002(3)	2536(7)	2979(4)
C4	1907(3)	4540(8)	2356(3)
C5	2417(2)	5308(8)	1765(3)
C6	3220(3)	4435(7)	1592(3)
C7	3918(3)	6026(8)	1888(3)
C8	4644(3)	4990(8)	2505(3)
C9	4581(3)	4784(8)	3638(3)
C10	3917(3)	3294(8)	3865(3)
C11	4131(3)	6819(8)	860(3)
C12	3696(3)	5411(7)	74(3)
C13	3928(3)	9137(9)	627(4)
C14	4100(3)	980(8)	3826(4)
C15	1149(3)	5779(10)	2502(4)
HO3	2150(3)	590(8)	1900(3)

Together with this, a small upfield shift was also observed in the signals of the CH<sub>3</sub>-15 methyl group in epoxide (3) as compared with that in (1).

The  $J_{7,11}$  SSCs were approximately the same, at 9–10 Hz, for all the lactones. Similar values are given in the literature [10] for heliangolides with a  $\beta$ -oriented C-13 methyl group. The signals of the H-6 lactone proton were observed in the form of a doublet of doublets with  $J_{5,6} = 11$ –11.5 Hz for (1) and  $J_{6,7} = 1.0$ –1.6 Hz for (3). A small value of  $J_{6,7}$  is characteristic for heliangolides [9, 10]. In the case of deacetylajanolide A (2),  $J_{6,7} = 7$  Hz, which probably shows a difference of the H6C6C7H7 torsional angle from those in (1) and (3). A result of the hydrolysis of (1) was epimerization of the CH<sub>3</sub>-13 methyl group and the formation of the thermodynamically more stable  $\alpha$ -epimer (2). Analogous transformations have been described in the literature for  $\alpha$ -santonin derivatives [12, 13].

TABLE 4. Coordinates of the Nonhydrogen Atoms of Structure (3) ( $\times 10^4$ )

Atom	3a			3b		
	x	y	z	x	y	z
O1	2920(1)	2382(2)	3708(1)	7869(1)	5670(1)	625(1)
O2	2460(1)	320(2)	3162(1)	7690(1)	5074(1)	1806(1)
O3	238(1)	7377(2)	4290(1)	6502(1)	10161(1)	-1442(1)
O4	4148(1)	5719(2)	4140(1)	7901(1)	6070(1)	-1421(1)
O5	6329(1)	5035(2)	4587(1)	9443(1)	4386(1)	-1506(1)
C1	1295(2)	6383(2)	4593(1)	7583(2)	9231(2)	-1096(1)
C2	2717(2)	6960(2)	4863(1)	8343(2)	8476(2)	-1638(1)
C3	3906(2)	5920(2)	4913(1)	9010(2)	7084(2)	-1374(1)
C4	3641(2)	4548(2)	5285(1)	9923(2)	7121(2)	-597(1)
C5	2942(2)	3478(2)	4939(1)	9474(2)	7062(2)	63(1)
C6	2234(2)	3414(2)	4128(1)	8010(2)	6942(2)	190(1)
C7	708(2)	3937(2)	4034(1)	7523(2)	8121(2)	670(1)
C8	-210(2)	3743(2)	3401(1)	5993(2)	8468(2)	415(1)
C9	-574(2)	5213(2)	3629(1)	5719(2)	9466(2)	-262(1)
C10	582(2)	6258(2)	3801(1)	6138(2)	8993(2)	-996(1)
C11	824(2)	1367(2)	3890(1)	7889(2)	7523(2)	1475(1)
C12	2118(2)	1251(2)	3540(1)	7797(2)	59712(2)	1355(1)
C13	-329(2)	602(2)	3431(1)	7088(2)	8023(2)	2085(1)
C14	1237(2)	6744(2)	3143(1)	5229(2)	7917(2)	-1439(1)
C15	4210(2)	4502(2)	6124(1)	11433(2)	7278(2)	-640(1)
C16	5405(2)	5215(2)	4060(1)	8266(2)	4736(2)	-1510(1)
C17	5457(2)	4882(3)	3254(1)	7042(2)	3807(2)	-1614(1)

In order to establish the orientation of the hydroxy group in (2) and the epoxy group in (3), and also to refine the spatial structures of (2) and (3), we subjected them to an x-ray structural investigation.

The molecules of (2) and (3) are shown in Figs. 1 and 2. The bond lengths and valence angles are close to the usual values [14] within the limits of accuracy. The values of the torsional angles at the C1—C10 and C4—C5 bonds — C2C1C10C9 and C3C4C5C6 [168.4 and  $-2.1^\circ$  in (2) and 158.2 and  $-2.4^\circ$  in (3a) and 159.1 and  $0.3^\circ$  in (3b), respectively] — unambiguously showed that compounds (2) and (3) were 1(10)E,4Z-germacranolides. The replacement of the C1—C10 double bond by an epoxide ring in (3) led to a decrease in the torsional angle at the substituted bond by 9.7 and  $8.8^\circ$  in (3a) and (3b), respectively (the C2C1C10C9 torsional angle in (1) is  $167.9^\circ$  [7]). The conformation of ring A in (2) and (3) is of the boat-chair type,  ${}^{14}D_1, {}_5D_{15}$ , that is the characteristic and most stable one for heliangolides.

A comparison of the intracyclic torsional angles in the two crystallographically independent molecules (3a) and (3b) (see Table 2) shows that the conformations of the boat-chair type,  ${}^{14}D_1, {}_5D_{15}$ , of their ten-membered rings do not differ qualitatively. The difference in the values of the corresponding torsional angles in ring A does not exceed  $6.0^\circ$ .

The germacrane skeleton is *trans*-linked with the  $\gamma$ -lactone ring in the (2) and (3) molecules (the torsional angles H6C6C7H7 are  $-112.3^\circ$  in (2) and  $-101.8$  and  $-98.6^\circ$  in the two crystallographically independent molecules (3a) and (3b), respectively). The hydroxy group at the C3 atom in (2) and the acetoxy group at the C3 atom in (3) have the  $\beta$ -orientation.

On the basis of what has been said above, for (2) we propose the structure of 3 $\beta$ -hydroxy-6,11 $\beta$ (H),7 $\alpha$ (H)-germacra-1(10)E,4Z-dien-6,12-olide, and for (3) — 3 $\beta$ -acetoxy-1 $\beta$ ,10 $\alpha$ -epoxy-6 $\beta$ (H)-7,11 $\alpha$ (H)-germacr-4Z-en-6,12-olide. The conformation of the lactone ring in these compounds is inverted in comparison with the usual one because of the conformational mobility of the ten-membered ring (torsional angles C5C6C7C8  $134.7^\circ$  in (2) and  $141.3$  and  $141.2^\circ$  in (3a) and (3b), respectively).

In structures (2) and (3) the  $\gamma$ -lactone ring assumes a conformation intermediate between a 7 $\beta$ -envelope and a 6 $\alpha$ ,7 $\beta$ -half-chair ( $C_s^7 = 2.3^\circ$  and  $C_2^{12} = 3.2^\circ$  in (2), and  $C_s^7 = 4.6$  and  $C_2^7 = 7.9^\circ$  in (3a)). In the (3b) molecule, ring B has the conformation almost of a 7 $\beta$ -envelope ( $C_s^7 = 0.2^\circ$ ).

## EXPERIMENTAL

Melting points were determined on a Kofler stage. IR spectra were taken on a UR-20 spectrometer (in  $\text{CHCl}_3$ ,  $\text{CCl}_4$ , or KBr). PMR spectra were recorded on Bruker WP 200 SY, Bruker WP 400 SY, and Bruker DRX-500 spectrometers (working frequencies for  $^1\text{H}$ : 200, 400, and 500 MHz, respectively, and for  $^{13}\text{C}$ : 125 MHz) in  $\text{CDCl}_3$ ,  $\text{C}_6\text{D}_6$ , and pyridine- $d_5$ . Internal standard TMS ( $\delta$ -scale). Mass spectra (EI, 70 eV) were obtained on a Finnigan MAT 8200 instrument (direct introduction; 70, 90, and 120°C). Optical rotations were measured on a Polamat A polarimeter (at 580 nm). For flash chromatography we used Chemapol 100/250 silica gel.

**3 $\beta$ -Hydroxy-6,11 $\beta$ (H),7 $\alpha$ (H)-germacra-1(10)E,4(5)Z-dien-6,12-olide (Deacetylanolide A (2))** was obtained by the method of [15].

A solution of 150 mg of ajanolide A in 20 ml of acetone was treated with 20 ml of a 1 M solution of  $\text{Na}_2\text{CO}_3$ . The reaction mixture was boiled for 15 min and was then cooled, treated with a 4% solution of HCl to neutrality, and extracted with ethyl acetate (3  $\times$  30 ml). The organic layers were combined, washed with water, dried with  $\text{Na}_2\text{SO}_4$ , and evaporated in a rotary evaporator. The residue (160 mg) was subjected to flash chromatography using mixtures of petroleum ether and EtOAc with a gradient increase in the latter. This gave 94 mg of colorless acicular crystals with mp 121–123°C (petroleum ether—EtOAc).  $[\alpha]_{580}^{25} +58^\circ$  (*c* 0.62;  $\text{CHCl}_3$ ).

IR spectrum ( $\text{CCl}_4$ ,  $\nu$ ,  $\text{cm}^{-1}$ ): 3606 (free OH), 3300–3600 (broad band), 1769 ( $\gamma$ -lactone), 1448, 1340, 1198, 1186, 964.

Mass spectrum (*m/z*, *I*(%)): 250M $[\text{M}]^+$  (51), 235(9), 232(20), 177(20), 169(28), 156(21), 153(15), 123(56), 121(25), 109(38), 95(100), 93(39). Found (*m/z*): 250.15659  $[\text{M}]^+$ . Calculated for  $\text{C}_{15}\text{H}_{22}\text{O}_3$ : 250.15688.

$^1\text{H}$ NMR spectrum ( $\text{CDCl}_3$ ,  $\delta$ , ppm, J, Hz, +25°C): 1.26 d, (3H, 7.5 Hz,  $\text{CH}_3$ (13)), 1.56 br.s (3H,  $\text{CH}_3$ (14)), 1.49 d (3H, 1.5 Hz  $\text{CH}_3$ (15)), 4.10 br.m (1H, H-3), 5.74 d (1H, 10 Hz, H-5), 5.72 d (1H, 10 Hz, H-1), 5.10 br.d (1H, 9 Hz, H-6).

$^1\text{H}$ NMR spectrum ( $\text{C}_6\text{D}_6$ ,  $\delta$ , ppm, J, Hz, +25°C): 1.21 d, (3H, 7.5 Hz,  $\text{CH}_3$ (13)), 1.68 br.s (3H,  $\text{CH}_3$ (14)), 1.49 d (3H, 1.5 Hz  $\text{CH}_3$ (15)), 4.10 br.m (1H, H-3), 5.74 d (1H, 10 Hz, H-5), 5.72 d (1H, 10 Hz, H-1), 5.10 br.d (1H, 9 Hz, H-6).

$^1\text{H}$ NMR spectrum ( $\text{CDCl}_3$ ,  $\delta$ , ppm., J, Hz, +25°C): 1.26 d (3H, 7, Hz,  $\text{CH}_3$ (13)), 1.56 br.s (3H,  $\text{CH}_3$ (14)), 1.68 d (3H, 1.5 Hz,  $\text{CH}_3$ (15)), 4.45 tr (1H, 3.3 Hz, H-3), 5.20 dq (1H, 10, Hz, H-5), 5.30 m (1H, H-1), 5.65 dd (1H, 10Hz, 7 Hz, H-6).

$^1\text{H}$ NMR spectrum (Py- $d_5$ ,  $\delta$ , ppm, J, Hz, +100°C): 1.18 d (3H, 7 Hz,  $\text{CH}_3$ (13)), 1.55 br. S (3H,  $\text{CH}_3$ (14)), 1.53 d (3H, 1.4 Hz,  $\text{CH}_3$ (15)), 4.45 tr, (1H, 3.5 Hz, H-3), 5.15 dq (1H, 11, Hz, 1.4 Hz, H-5), 5.35 br.tr (1H, 8.5 Hz, H-1), 5.70 dd (1H, 10 Hz, 7 Hz, H-6).

**3 $\beta$ -acetoxy-1 $\beta$ ,10 $\alpha$ -epoxy-6 $\beta$ (H)-7,11 $\alpha$ (H)-germacr-4Z-en-6,12-olide (Ajanolide A Epoxide (3))** was obtained by the procedure of (16).

To a solution of 150 mg of ajanolide A (1) in 20 ml of  $\text{CHCl}_3$  was added a freshly prepared solution of peracetic acid in chloroform, and the reaction mixture was left for a day. Then it was treated with a 5% solution of  $\text{NaHCO}_3$  to neutrality and extracted with EtOAc (3  $\times$  40 ml). The organic layer was washed with water, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated in a rotary evaporator. The residue (160 mg) was subjected to flash chromatography on Chemapol silica gel (ratio of total material to support 1:50). We isolated 45 mg (28% yield) of white acicular crystals of (3) with mp 136–138°C (petroleum ether—EtOAc),  $[\alpha]_{580}^{26} +95.2^\circ$  (*c* 0.168;  $\text{CHCl}_3$ ) and 103 mg of the initial substance (1).

IR spectrum ( $\text{CCl}_4$ ,  $\nu$ ,  $\text{cm}^{-1}$ ): 1780 ( $\gamma$ -actone), 1750, 1253, 1210 (OAc), 1675 (C=C), 1165, 1105, 1030, 995, 965, 870.

Mass spectrum (*m/z*, *I*, (%)): 309  $[\text{M}+1]^+$  (0.4), 293(1.2), 266(2.5), 248(13.3), 233(3.2), 220(5.5), 205(5.3), 193(5.8), 192(5.1), 182(3.2), 180(5.1), 175(8.8), 165(10.5), 149(15.7), 135(12.6), 123(17.8), 122(13.2), 11(12.9), 109(17.5), 97(19.4), 95(28), 81(15.1), 69(24.7), 55(31.2), 43(100), 41(24.4).

$^1\text{H}$ NMR spectrum ( $\text{C}_6\text{D}_6$ ,  $\delta$ , ppm, J, Hz, +25°C): 0.90 d, (3H, 7.5 Hz,  $\text{CH}_3$ (13)), 1.19 s (3H,  $\text{CH}_3$ (14)), 1.53 d (3H, 1.5 Hz  $\text{CH}_3$ (15)), 1.74 s (3H, OAc), 2.10 ddd (1H, 15 Hz, 4.5 Hz, 4.5 Hz, H-2a), 1.45 ddd (1H, 15 Hz, 10 Hz, 2.0 Hz, H-2b), 2.20 dq (1H, 9 Hz, 7.5 Hz, H-11), 2.40 dd (1H, 10 Hz, 4.5 Hz, H-1), 4.83 dq (1H, 11/5 Hz, 1/5 Hz, H-5), 4.87 dd (1H, 4.5 Hz, 2.0 Hz, H-3), 5.26 d (1H, 11.5 Hz, H-6).

$^{13}\text{C}$ NMR spectrum ( $\text{C}_6\text{D}_6$ ,  $\delta$ , ppm, J, Hz, +25°C): 10.38 q, (c-13), 16.68 q, 20.64 q (c-17, methyl of an acetate group), 23.30 q, 24.38 tr, 29.61 tr, 35.87 d (C-11), 40.67 Er, 44.67 d, 72.97 d (C-3), 79.31 d (C-6), 59.80 d (C-1), 125.39 d (C-5), 138.17 s (C-4), 59.30 s (C-10), 168.85 s (C-16, carbonyl of an acetate group), 177.93 s (C-12).

Elementary analysis. Found, %: C 66.33; H 7.75. Calculated for  $\text{C}_{17}\text{H}_{24}\text{O}_5$ , %: C 66.21; H 7.85.

**X-Ray Structural Experiment.** The cell parameters and the intensities of the reflections from crystals of (2) and (3) were measured on a Siemens SMART CCD automatic four-circle diffractometer at  $T = -100^\circ\text{C}$  (MoK $\alpha$ , graphite

monochromator,  $\theta/2\theta$  scanning,  $2\theta < 58^\circ$ ). The crystals of (2) were monoclinic,  $a=16.983(5)\text{\AA}$ ,  $b=6.283(2)\text{\AA}$ ,  $c=13.310(4)\text{\AA}$ ,  $\beta=96.474(7)^\circ$ ,  $M=250.3$ ,  $d_{\text{calc}}=1.178\text{ g/cm}^3$ ,  $Z=4(\text{C}_{15}\text{H}_{22}\text{O}_3)$ , sp.gr. C2. The crystals of (3) were monoclinic  $a=9.8151(9)\text{\AA}$ ,  $b=9.6133(9)$ ,  $c=17.8963(17)\text{\AA}$ ,  $\beta=99.69(2)^\circ$ ,  $M=308.4$ ,  $d_{\text{calc}}=1.230\text{ g/cm}^3$ ,  $Z=4(\text{C}_{17}\text{H}_{24}\text{O}_5)$  sp.gr. P2<sub>1</sub>.

The structures were interpreted by the direct method and were refined by full-matrix MLS in the anisotropic approximation for the nonhydrogen atoms. The H atom of hydroxy groups were revealed in a difference synthesis, and the others are given geometrically. The final divergence factors were  $R = 0.0704$  and  $R_w = 0.1737$  for 2328 independent reflections with  $I > 2\sigma$  in structure (2), and  $R = 0.0370$  and  $R_w = 0.0837$  for 7384 independent reflections with  $I > 2\sigma$  in structure (3).

All the calculations were made by the SHELXTL and SHELXL-95 program packets on a Silicon Graphics work station. The coordinates of the atoms of structures (2) and (3) are given in Tables 3 and 4.

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