

**CRYSTAL STRUCTURE OF THE NATIVE SESQUITERPENE LACTONE  
8 $\alpha$ -ANGELOYLOXY-10 $\beta$ ,11 $\alpha$ -DIACETOXY-SLOV-3-ENOLIDE\***

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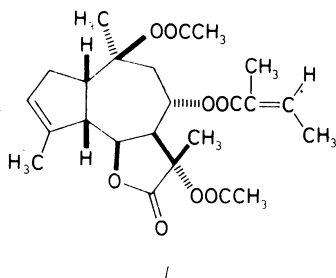
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Received March 16, 1989

Accepted June 16, 1989

The X-ray structural analysis of 8 $\alpha$ -angeloyloxy-10 $\beta$ ,11 $\alpha$ -diacetoxy-slov-3-enolide (*I*) confirms the structure of *I* deduced from spectral data and from the X-ray analysis of its derivative *II*. The stereostructure of *I* is discussed and compared with that of *II* and *III*.

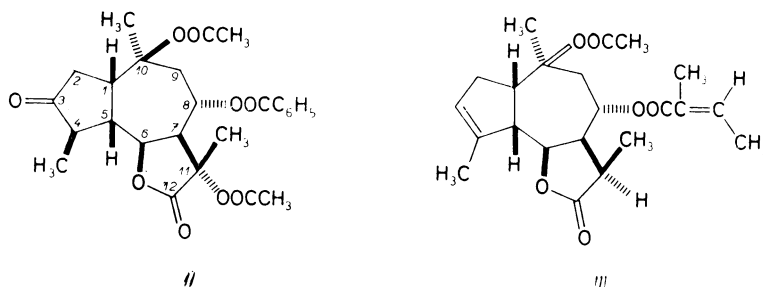
A naturally occurring sesquiterpene lactone 8 $\alpha$ -angeloyloxy-10 $\beta$ ,11 $\alpha$ -diacetoxy-slov-3-enolide (*I*) was isolated among other lactones from *Laserpitium siler* L. (*Umbelliferae* family, *Laserpitieae* tribe) and originally was given a name acetylismontanolide<sup>1</sup>. On the basis of physical methods, mainly <sup>1</sup>H NMR spectroscopy, the structure *I* was proposed for this compound<sup>2</sup> indicating that it belongs to a novel stereochemical group of 1 $\beta$ H,5 $\beta$ H,6 $\alpha$ H,7 $\alpha$ H-guaian-6,12-olides for which we proposed the name slovanolides<sup>3</sup>.



Confirmation of the structure *I* was sought through crystallographic analysis, but any attempt to solve the crystal structure of the native compound failed. An indirect evidence for the correct assignment of structure *I* to acetylismontanolide came from the X-ray analysis<sup>4</sup> of its derivative *II*, prepared by a multistep reaction sequence

\* Part CCCI in the series On Terpenes; Part CCC: Collect. Czech. Chem. Commun. 54, 1919 (1989).

in which an inversion at the chiral centers should not take place. X-Ray analysis of *II* not only confirmed the presumed structure of *I* but also allowed us to correct the structure of closely related lactone *III*, isolated from *Laserpitium marginatum*, for which an X-ray analysis was also carried out, but the results were incorrectly interpreted<sup>5</sup>. We now report the results of a successful X-ray analysis of *I*. The inherent problem of solving a structure in the symmorphic space group (*A2*) was compounded, in this case, by the existence of high thermal motions or conformational disorder in the angelate group attached to C(8).



## EXPERIMENTAL

### Crystal Data

$C_{24}H_{32}O_8$ , m.p. 134°C, monoclinic, space group *A2*,  $a = 8.499(1)$ ,  $b = 8.408(1)$ ,  $c = 35.924(7)$  Å,  $\beta = 105.99(1)^\circ$ ,  $V = 2467.7(7)$  Å<sup>3</sup>,  $D_m = 1.20$  (by flotation in aqueous solution of KI),  $D_c = 1.21$  g/cm<sup>3</sup> for  $Z = 4$ .

### Crystallographic Measurements

Preliminary Weissenberg photographs indicated monoclinic centered cell, and since the compound is an optically active natural product the space group is *A2*.

A crystal of approximate dimensions 0.3 × 0.3 × 0.4 mm was used for data collection on a Syntex P2<sub>1</sub> diffractometer using graphite monochromated  $CuK_\alpha$  radiation. Lattice constants and an orientation matrix were obtained from a least-square fit of 15 centered reflections. Intensities were measured using  $\theta - 2\theta$  scan technique, with the scan rate depending directly on the net count obtained on rapid pre-scans for each reflection. Two standard reflections were monitored after collection of every 100 reflections as a check of electronic reliability and crystal stability, and no abnormalities were noted. One fourth of the reciprocal sphere was collected such that  $h$  and  $k$  were non-negative. 1791 unique reflections measured of which 146 were considered unobserved [ $I < 2\sigma(I)$ ]. The background and integrated intensity for each reflection were evaluated from a profile analysis according to Lehmann and Larsen<sup>6</sup> using the PRAN program<sup>7</sup>. Lorentz and polarization factors were applied in reducing the intensities to structure factor amplitudes, but no absorption correction was deemed necessary [ $\mu(CuK_\alpha) = 0.76$  mm<sup>-1</sup>]. All data having  $I \geq 2\sigma(I)$  were used in least squares refinement, with the exception of two low-angle reflections found to be poorly determined. Anomalous dispersion corrections were applied to the scattering factors of the oxygen and carbon atoms.

## Structure Analysis

The structure was solved by direct methods only with considerable difficulty. Initially no meaningful structural models were obtained using MULTAN (ref.<sup>8</sup>) packages. Several attempts on the evaluation of the *E*-values were made by providing structural information as randomly oriented and randomly positioned molecular fragments. Finally, almost complete molecular fragment of the lactone<sup>4</sup> *III* gave encouraging values of the figures of merit, but still no chemically reasonable model could be deduced from the *E*-map. At this point the coordinates of the top 7 peaks were input to DIRDIF (ref.<sup>9</sup>) which in two successive calculations revealed all non-hydrogen atoms present in the asymmetric part of the unit cell. The usual sequence of isotropic and anisotropic full matrix least-squares was followed. The angelate group attached to C(8) showed a geometry which was obviously not sensible from any chemical argument, and could only be attributed to some statistical disorder or high thermal motions of this group. No reasonable disorder model could be found. Therefore, at the final stages of the refinement an idealized geometry was set up for the  $-\text{C}(\text{CH}_3)=\text{CH}.\text{CH}_3$  group of the angelate side chain and this group was further refined as a "rigid group". The hydrogen atoms were placed at calculated positions and were subjected to constraint refinement, with the exception of hydrogen atoms from the angelate group the positions of which were not included in the structure factor calculations. All H-atoms included in the refinement were assigned a common isotropic temperature factor refined to  $U = 0.121 \text{ \AA}^2$ . At the end of the refinement an empirical isotropic extinction parameter  $x$  was introduced to correct the calculated structure factors by multiplying them by a factor  $1 - xF_c^2/\sin \Theta$  and it refined to a value  $1.3(1) \cdot 10^{-6}$ . The function minimized was  $\sum(|F_o| - |F_c|)^2$  with  $w = 1/[\sigma^2 F_o + 0.001 F_o^2]$  where  $\sigma$  is the standard deviation of the observed amplitudes, based on counting statistics. Convergence attained at  $R = 0.058$  ( $wR = 0.086$ ) for 1 642 observed reflections. The final difference map showed minima and maxima ranging from  $-0.002$  to  $+0.25 \text{ e \AA}^{-3}$ , the latter lying in the near vicinity of atoms C(19), C(20), C(21) and C(22). The refinement was carried out using SHELX-76 program<sup>10</sup>.

Final positional parameters for non-hydrogen atoms are listed in Table I. Tables of observed and calculated structure factors are available from the author (U.R.) on request.

## RESULTS AND DISCUSSION

The X-ray study of  $8\alpha$ -angeloyloxy- $10\beta,11\alpha$ -diacetoxy-slov-3-enolide (*I*) confirms the structure deduced from spectral techniques<sup>2,3</sup> and from X-ray analysis<sup>4</sup> of its derivative *II*. The stereostructure of the molecule of *I* is depicted in Fig. 1, which is an ORTEP (ref.<sup>11</sup>) drawing. No absolute configuration assignments have been made by anomalous dispersion method. The absolute configuration shown in Fig. 1 has been deduced earlier<sup>2</sup>. The title compound is a guaianolide type sesquiterpene lactone, containing a five-membered ring *cis*-fused to a seven membered ring and a *cis*-fused (at C(6)—C(7))  $\gamma$ -lactone. The three ring skeleton is of the *cis-transoid-cis* configuration, with hydrogen atoms at C(1) and C(5)  $\beta$ -, and at C(6) and C(7)  $\alpha$ -oriented. The solid state conformation is described by torsion angles and puckering parameters<sup>12</sup> depicted in Fig. 2 and is compared with the conformation of closely related compounds *II* and *III* in Table II. The puckering parameters for cyclopentene indicate a non-planar conformation (average torsion angle moduli is  $24^\circ$ ), intermediate between C(1) $\alpha$ -envelope and C(1) $\alpha$ ,C(5) $\beta$ -half chair. The five-membered ring

puckering coordinates  $\phi_m$  and  $\Delta$  were calculated from the endocyclic torsion angles  $\phi_j$  by using a method introduced by Altona, Geise and Romers<sup>12</sup> which is summarized by equation

$$\phi_j = \phi_m \cos(\Delta + 4\pi_j/5), \quad j = 0, 1, \dots, 4,$$

where  $\phi_m$  is the amplitude and  $\Delta$  is the phase angle of the puckering.

The seven-membered ring approximates the twist chair conformation, although with considerable deviations from the ideal form. As a measure of the deviations the sum ( $\Sigma$ ) of the absolute values of differences of symmetry related torsion angles is used<sup>13</sup>.  $\Sigma_2$  and  $\Sigma_s$  represent deviations from ideal  $C_2$  and  $C_s$  symmetry of the seven-membered ring. For the ideal boat and chair forms the ring contains a mirror plane with  $\Sigma_s = 0^\circ$  and  $\Sigma_2 = 114^\circ$  and  $205^\circ$ , respectively. For the ideal twisted form the ring contains a two-fold axis;  $\Sigma_2 = 0^\circ$  and  $\Sigma_s = 215^\circ$  and  $141^\circ$  for the twisted boat and chair forms, respectively. The  $\Sigma_2$  and  $\Sigma_s$  parameters are calculated in a manner described by McPhail and Sim<sup>13</sup>.

$$\Sigma_2 = (|\phi_1 - \phi_6| + |\phi_2 - \phi_5| + |\phi_3 - \phi_4|),$$

$$\Sigma_s = (|\phi_6 + \phi_7| + |\phi_1 + \phi_5| + |\phi_2 + \phi_4| + |\phi_3|)$$

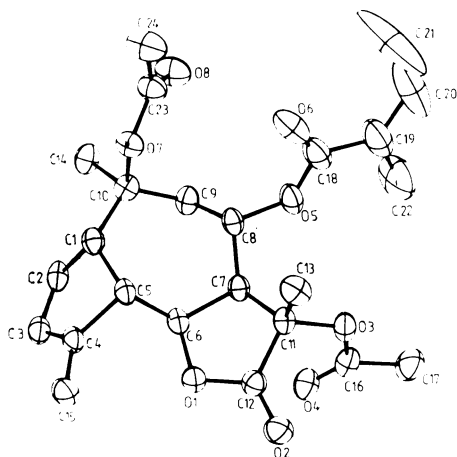


FIG. 1

ORTEP (ref.<sup>11</sup>) view of the molecule *I* showing the numbering scheme. Thermal ellipsoids are drawn at 25% probability level

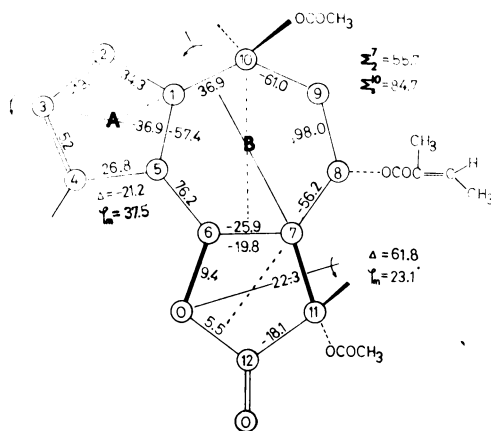


FIG. 2

Endocyclic torsion angles ( $^\circ$ ) and puckering parameters describing conformation of the three-ring-skeleton in *I*. Best preserved mirror and two-fold rotational symmetries are indicated by dashed and solid lines, respectively

The  $\phi_1 - \phi_7$  terms are the torsion angles for the seven-membered ring and appear in sequential order in Table II. The  $\Sigma$  value for  $C_2$  symmetry is  $55.7^\circ$  for the molecule of *I*, which may be compared with the ideal twist chair value of  $0.0^\circ$  and with the

TABLE I

Final fractional coordinates and equivalent isotropic thermal parameters with e.s.d.'s of the refined parameters in parentheses for the molecule *I*.  $U_{\text{eq}} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$

Atom	$x/a$	$y/b$	$z/c$	$U_{\text{eq}}, \text{\AA}^2$
C(1)	-0.4546(6)	-0.2892(8)	-0.2894(1)	60(3)
C(2)	-0.3633(7)	-0.2016(9)	-0.2526(2)	71(2)
C(3)	-0.4864(8)	-0.2064(9)	-0.2292(1)	73(2)
C(4)	-0.6358(7)	-0.2357(8)	-0.2515(1)	64(2)
C(5)	-0.6339(6)	-0.2393(8)	-0.2940(1)	56(2)
C(6)	-0.6765(6)	-0.0692(8)	-0.3096(1)	59(2)
C(7)	-0.7019(6)	-0.0349(9)	-0.3534(1)	56(2)
C(8)	-0.6115(6)	-0.1488(9)	-0.3721(1)	60(2)
C(9)	-0.4292(7)	-0.1518(9)	-0.3517(2)	69(2)
C(10)	-0.3770(6)	-0.2870(9)	-0.3233(2)	64(2)
C(11)	-0.8885(6)	-0.0243(8)	-0.3695(1)	57(2)
C(12)	-0.9459(7)	0.0148(8)	-0.3341(2)	61(2)
C(13)	-0.9735(7)	-0.1790(10)	-0.3867(2)	73(2)
C(14)	-0.1915(7)	-0.3005(10)	-0.3073(2)	80(2)
C(15)	-0.7864(9)	-0.2599(10)	-0.2381(2)	80(2)
C(16)	-0.9177(7)	0.2488(10)	-0.3880(2)	78(3)
C(17)	-0.9890(12)	0.3558(14)	-0.4220(3)	112(4)
C(18)	-0.6746(10)	0.1924(17)	-0.4400(2)	98(4)
C(19)	-0.7018(11)	-0.1116(15)	-0.4785(1)	142(7)
C(20)	-0.7247(11)	-0.1928(15)	-0.5116(1)	221(21)
C(21)	-0.7357(10)	-0.3745(15)	-0.5114(1)	341(21)
C(22)	-0.6882(11)	0.0712(15)	-0.4786(1)	200(15)
C(23)	-0.3891(8)	-0.4939(10)	-0.3731(2)	78(3)
C(24)	-0.4566(13)	-0.6555(12)	-0.3854(3)	111(4)
O(1)	-0.8276(5)	-0.0199(0)	-0.3017(1)	69(1)
O(2)	-1.0777(5)	0.0618(8)	-0.3336(1)	78(2)
O(3)	-0.9423(4)	0.0956(8)	-0.3991(1)	73(2)
O(4)	-0.8475(6)	0.2900(8)	-0.3563(1)	87(2)
O(5)	-0.6367(5)	-0.0908(8)	-0.4115(1)	82(2)
O(6)	-0.6882(8)	-0.3367(13)	-0.4343(2)	123(3)
O(7)	-0.4398(4)	-0.4415(7)	-0.3433(1)	65(1)
O(8)	-0.3001(6)	-0.4251(9)	-0.3883(1)	101(2)

$\Sigma$  values of  $36.9^\circ$  and  $37.6^\circ$  observed in crystal structures of closely related compounds *II* and *III*, respectively. In all these compounds the approximate two-fold axis passes through C(7) and the midpoint of the C(1)—C(10) bond. Such a conformation enables the formation of the fully-equatorial *cis*-fused  $\gamma$ -lactone at position C(6)—C(7) and reduces to its lowest value the strain energy associated with the axial substituents at C(1) and C(10). A perfect  $C_2$  symmetry in the cycloheptane ring is destroyed in part by a *cis*-fusion with both 5-membered rings. Similar, though much less deformed conformation of cycloheptane was found in hysterin<sup>14</sup>, a pseudo-guaianolide of ambrosanolide type, with ring junctions C(1)—C(5) *trans* and C(6)—C(7) *cis*. In this context it might be worth to mention that the stereostructural type

TABLE II  
Endocyclic torsion angles ( $^\circ$ ) in the three-ring system of slovanolides

Atoms	Compound		
	<i>I</i>	<i>II</i>	<i>III</i>
5-Membered ring			
C(5)—C(1)—C(2)—C(3)	34.3(6)	38.1(6)	33.0
C(1)—C(2)—C(3)—C(4)	—19.0(7)	—18.0(6)	—17.8
C(2)—C(3)—C(4)—C(5)	—5.2(7)	—9.0(6)	—5.8
C(3)—C(4)—C(5)—C(1)	26.8(6)	32.1(6)	26.9
C(4)—C(5)—C(1)—C(2)	—36.9(6)	—43.3(5)	—36.6
10-Membered ring			
C(10)—C(1)—C(5)—C(6)	—57.4(6)	—58.8(6)	—57.1
C(1)—C(5)—C(6)—C(7)	76.2(5)	78.4(6)	80.9
C(5)—C(6)—C(7)—C(8)	—25.9(5)	—34.7(6)	—34.1
C(6)—C(7)—C(8)—C(9)	—56.2(7)	—45.0(6)	—52.4
C(7)—C(8)—C(9)—C(10)	98.0(7)	93.9(6)	96.9
C(8)—C(9)—C(10)—C(1)	—61.0(6)	—69.9(7)	—60.4
C(9)—C(10)—C(1)—C(5)	36.9(6)	44.9(7)	37.0
$\gamma$ -Lactone ring			
O(1)—C(6)—C(7)—C(11)	—19.8(5)	—25.5(5)	—22.2
C(6)—C(7)—C(11)—C(12)	22.3(6)	27.5(6)	22.5
C(7)—C(11)—C(12)—O(1)	—18.1(5)	—20.0(5)	—15.2
C(11)—C(12)—O(1)—C(6)	5.5(5)	4.2(6)	1.4
C(12)—O(1)—C(6)—C(7)	9.4(5)	13.8(5)	13.3

of the  $1\beta H, 5\beta H, 6\alpha H, 7\alpha H$ -guaian-6,12-olides represented by lactones *I*, *II* and *III* corresponds to the stereostructural type of  $5\beta(CH_3), 6\alpha H, 7\alpha H$ -pseudoguaian-6,12-olides to which hysterin belongs.

The  $\gamma$ -lactone ring is relatively flat and adopts conformation intermediate between  $7\alpha, 11\beta$ -half chair and  $7\alpha$ -envelope. The best preserved symmetry element, the two-fold axis, runs through the midpoint of the C(7)—C(11) bond. Several sesquiterpene  $\gamma$ -lactones have been reported to adopt a half-chair conformation. However, in a vast majority of examples previously reported atoms at the ring fusion, i.e. C(7) and C(6) or C(7) and C(8), were out of the ring plane, while in *I* it is C(11) which together with C(7) is displaced above and below the plane, respectively. This mode of puckering, which seems to be characteristic for *cis*-fused  $\gamma$ -lactones containing an esterified hydroxyl function<sup>15,16</sup> at C(11), is also observed in *II*, while in *III*, which lacks this hydroxyl group, the ring approximates a  $7\alpha$ -envelope conformation.

As expected from similarities in molecular formulas, and as it follows from Table II the molecules of *I*, *II*, and *III* are very similar in conformation. The molecules of native lactones *I* and *III* which differ only in the substitution at C(11) show in the solid state different orientation of the angeloyloxy substituent at C(8). A superposition of the two molecules is shown in Fig. 3. There is no possibility of hydrogen bonding in the crystals of *I* and the packing of the molecules is entirely due to van der Waals interactions.

*U.R. wishes to thank the MEN for financial support of a part of this work (Problem number: RP II 10.1.2.).*

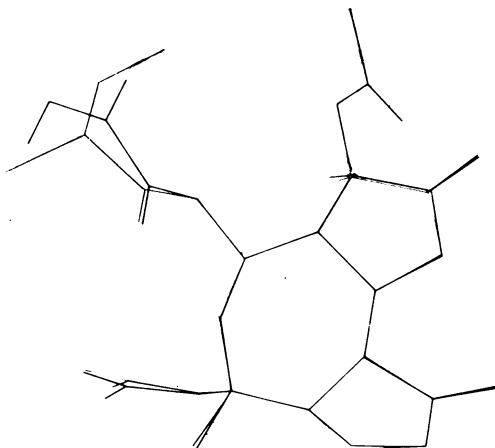


FIG. 3

Crystallographic fitting of the carbocyclic rings of the molecules *I* (thick lines) and *III*

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