19. Metabolites of Microorganisms. 162nd Communication[1]). The Crystal and Molecular Structure of Lysolipin I

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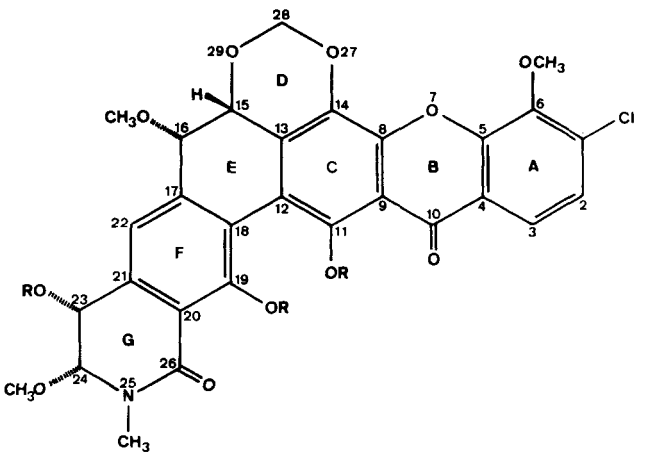
Summary

The triacetate of the antibiotic lysolipin (**1**) crystallizes in the space group $P2_1$, $a = 11.059$, $b = 21.453$, $c = 8.423$ Å, $\beta = 109.76°$. X-ray analysis was used to determine the structure of this compound.

In a recent paper [2] the isolation and characterization of the antibiotic lysolipin (**1**) from a *streptomyces* culture was described. The compound crystallized in long, bright yellow needles and had the composition $C_{29}H_{24}ClNO_{11}$, confirmed by molecular peaks at $m/e = 597$ and 599 in the mass spectrum. Since NMR. and IR. spectra indicated a novel and rather complicated polycyclic structure, we decided to determine it by X-ray analysis.

Whereas the free antibiotic (**1**, R = H) gave long, thin needles not suitable for a diffraction study, the triacetate, R = $COCH_3$, could be crystallized from acetone/water as an acetone solvate, forming prisms of considerable size.



[1]) 161st communication, see [1].

Crystallographic data. – Lysolipin (**1**) triacetate, $C_{35}H_{30}ClNO_{14} \cdot (CH_3)_2CO$, Mol.-Wt. = 724 (the crystals contain one molecule of acetone per asymmetric unit). Monoclinic, $a = 11.059(2)$, $b = 21.453(3)$, $c = 8.423(2)$ Å, $\beta = 109.76(3)°$, $U = 1881$ Å^3, $Z = 2$. Space group $P2_1(C_2^2)$, $D_x = 1.38$. Cell constants were obtained from diffractometer measurements (Mo$K\alpha$ radiation).

Data collection. – Intensities were measured with a computer-controlled diffractometer (*Nonius* CAD4), using graphite-monochromatized Mo$K\alpha$ radiation. In the range $\theta < 24°$ all reflections were measured, in the range $24° < \theta < 28°$ only those judged by a preliminary scan to have significant intensity. The 4660 intensity measurements obtained were processed in the usual way, yielding 3438 unique reflections with $F_o > 3\sigma(F_o)$. Absorption corrections were not applied ($\mu_{Mo} = 1.9$ cm^{-1}).

Structure analysis. – The elucidation of the crystal structure was achieved in several steps. The first attempt to solve the crystal structure by direct methods using the program MULTAN

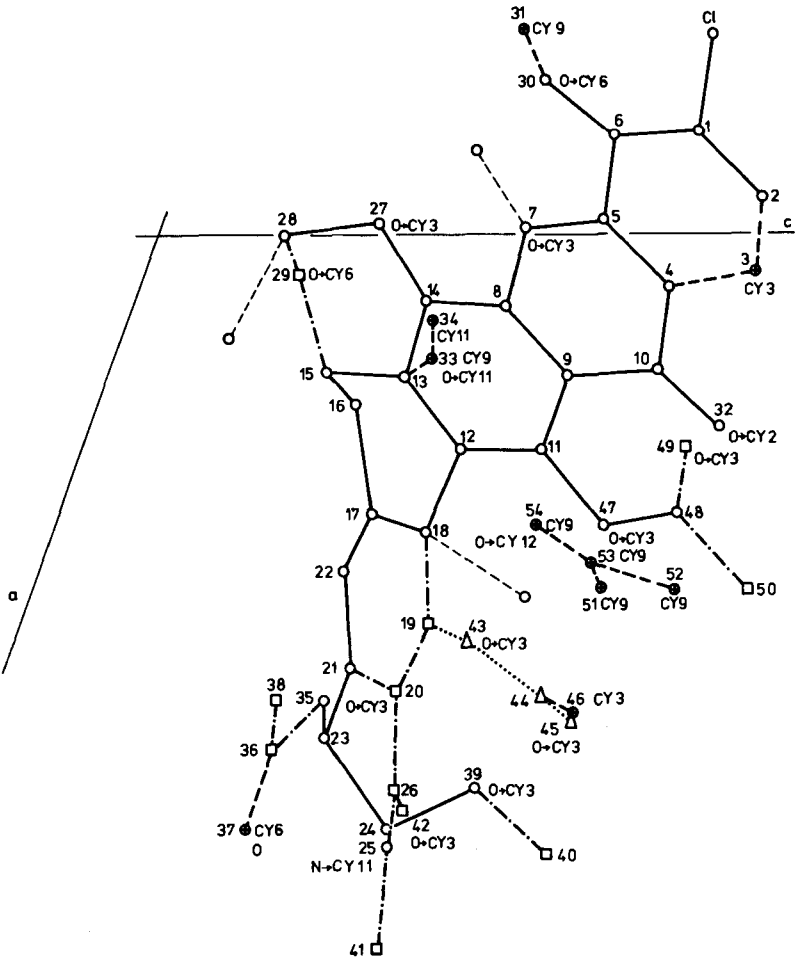


Fig. 1. *Progress of the structure determination.* ○: atoms found from MULTAN 74; □: atoms added from first phase refinement cycle; △: atoms added from second phase refinement cycle; ⊕: atoms found in later stages. For these atoms it is indicated at which least-squares refinement cycle they were included.

74 [3] produced a 23 atom fragment which could not be further developed by phase refinement. A second attempt, with a different choice of origin defining reflections, resulted in a similar fragment of 34 atoms, translated by $z=1/2$. This fragment (see Fig. 1) was further developed by phase refinement. In a first cycle, 11 additional peaks could be assigned, and 3 of the previously accepted peaks had to be discarded. In the second cycle, 3 new peaks were accepted to form a 45 atom fragment. At this stage a series of least-squares refinement cycles was begun, additional atoms being inserted from time to time (Fig. 1) on the basis of difference syntheses. In all, 18 cycles of block-diagonal least-squares analysis and 4 difference maps were computed. The final least-squares cycle based on the 3438 reflections with $F_o > 3\sigma(F_o)$ led to the coordinates listed in Table 1. All non-hydrogen atoms were assigned anisotropic temperature factors. Many hydrogen atoms could be located in the difference maps, but calculated positions (assumptions: C–H, equal angles with the attached bonds, H–C–H, local C_{2v} symmetry, bond angle 109°, H–C distance 1.1 Å, methyl groups staggered) were used and not refined. The final R factor was 0.067.

Results. – Fractional coordinates and calculated hydrogen atom positions are given in Tables 1 and 2. Standard deviations were estimated by inversion of the least-squares normal equations. Bond lengths and angles are given in Fig. 2. The

Table 1. *Fractional coordinates* (estimated standard deviation $\times 10^4$ in parentheses)

	X		Y		Z			X		Y		Z	
Cl	−0.2791	(2)	0.0000	(–)	0.8412	(3)	C28	0.0023	(7)	0.2433	(5)	0.2305	(9)
C1	−0.1434	(7)	0.0470	(3)	0.8743	(10)	O29	0.0546	(4)	0.3030	(3)	0.2723	(6)
C2	−0.0538	(7)	0.0501	(4)	1.0363	(10)	O30	−0.2206	(5)	0.0738	(3)	0.5808	(7)
C3	0.0542	(7)	0.0857	(4)	1.0632	(10)	C31	−0.2915	(9)	0.1285	(5)	0.5106	(12)
C4	0.0733	(6)	0.1188	(3)	0.9296	(9)	O32	0.2693	(5)	0.1611	(3)	1.0998	(6)
C5	−0.0190	(6)	0.1157	(3)	0.7707	(9)	O33	0.1727	(5)	0.3835	(3)	0.5594	(7)
C6	−0.1320	(6)	0.0790	(3)	0.7399	(10)	C34	0.1170	(17)	0.4362	(6)	0.5318	(18)
O7	−0.0090	(4)	0.1467	(2)	0.6360	(5)	O35	0.6553	(4)	0.4821	(2)	0.5761	(6)
C8	0.0971	(5)	0.1827	(3)	0.6553	(8)	C36	0.7244	(7)	0.5254	(3)	0.5276	(9)
C9	0.1988	(5)	0.1885	(3)	0.8081	(8)	O37	0.8280	(5)	0.5158	(3)	0.5179	(8)
C10	0.1903	(6)	0.1568	(3)	0.9587	(8)	C38	0.6521	(8)	0.5864	(4)	0.4928	(10)
C11	0.3043	(5)	0.2265	(3)	0.8083	(7)	O39	0.7748	(4)	0.4347	(2)	0.9001	(6)
C12	0.3079	(5)	0.2564	(3)	0.6663	(7)	C40	0.8645	(8)	0.4278	(4)	1.0656	(9)
C13	0.1963	(5)	0.2537	(3)	0.5207	(7)	C41	1.0022	(6)	0.3358	(4)	0.8369	(10)
C14	0.0936	(5)	0.2161	(3)	0.5136	(7)	O42	0.8138	(4)	0.2474	(2)	0.7748	(6)
C15	0.1869	(5)	0.2979	(4)	0.3775	(7)	O43	0.5739	(3)	0.2233	(2)	0.7912	(5)
C16	0.2378	(6)	0.3613	(3)	0.4499	(8)	C44	0.6522	(5)	0.2221	(3)	0.9574	(8)
C17	0.3791	(5)	0.3507	(3)	0.5500	(7)	O45	0.6889	(4)	0.2685	(2)	1.0377	(5)
C18	0.4131	(5)	0.2971	(3)	0.6511	(7)	C46	0.6815	(8)	0.1569	(4)	1.0172	(11)
C19	0.5436	(5)	0.2817	(3)	0.7162	(7)	O47	0.4069	(3)	0.2323	(2)	0.9595	(5)
C20	0.6381	(5)	0.3205	(3)	0.6963	(7)	C48	0.3863	(6)	0.2688	(3)	1.0809	(7)
C21	0.6023	(5)	0.3765	(3)	0.6105	(7)	O49	0.2970	(4)	0.3023	(3)	1.0549	(6)
C22	0.4721	(6)	0.3909	(3)	0.5332	(8)	C50	0.4946	(7)	0.2605	(5)	1.2461	(8)
C23	0.7085	(5)	0.4198	(3)	0.6039	(8)	C51	0.4958	(14)	−0.0808	(6)	0.9920	(20)
C24	0.8198	(6)	0.4146	(3)	0.7698	(9)	C52	0.4950	(15)	0.0214	(7)	1.1264	(18)
N25	0.8626	(5)	0.3498	(3)	0.7861	(7)	C53	0.4567	(9)	−0.0166	(6)	0.9646	(13)
C26	0.7787	(5)	0.3017	(3)	0.7578	(8)	O54	0.4065	(–)	0.0057	(–)	0.8418	(–)
O27	−0.0143	(4)	0.2130	(3)	0.3743	(5)							

Table 2. *Calculated hydrogen atom fractional coordinates*

	X	Y	Z		X	Y	Z
H2	−0.069	0.025	1.140	H402	0.949	0.455	1.075
H3	0.125	0.089	1.190	H403	0.889	0.378	1.086
H15	0.244	0.280	0.305	H411	1.013	0.285	0.843
H16	0.227	0.394	0.348	H412	1.049	0.356	0.962
H22	0.444	0.433	0.460	H413	1.038	0.356	0.744
H23	0.741	0.406	0.500	H461	0.744	0.158	1.150
H24	0.898	0.445	0.766	H462	0.729	0.134	0.940
H281	0.068	0.216	0.188	H463	0.591	0.134	1.005
H282	−0.091	0.248	0.133	H501	0.474	0.291	1.339
H311	−0.358	0.116	0.385	H502	0.583	0.275	1.227
H312	−0.224	0.164	0.503	H503	0.498	0.212	1.283
H313	−0.345	0.143	0.593				
H341	0.074	0.444	0.628	H511	0.542	−0.088	1.128
H342	0.042	0.433	0.406	H512	0.563	−0.091	0.926
H343	0.188	0.471	0.535	H513	0.410	−0.110	0.945
H381	0.711	0.620	0.454	H521	0.543	−0.011	1.233
H382	0.637	0.601	0.608	H522	0.410	0.041	1.143
H383	0.561	0.578	0.392	H523	0.563	0.057	1.120
H401	0.819	0.444	1.155				

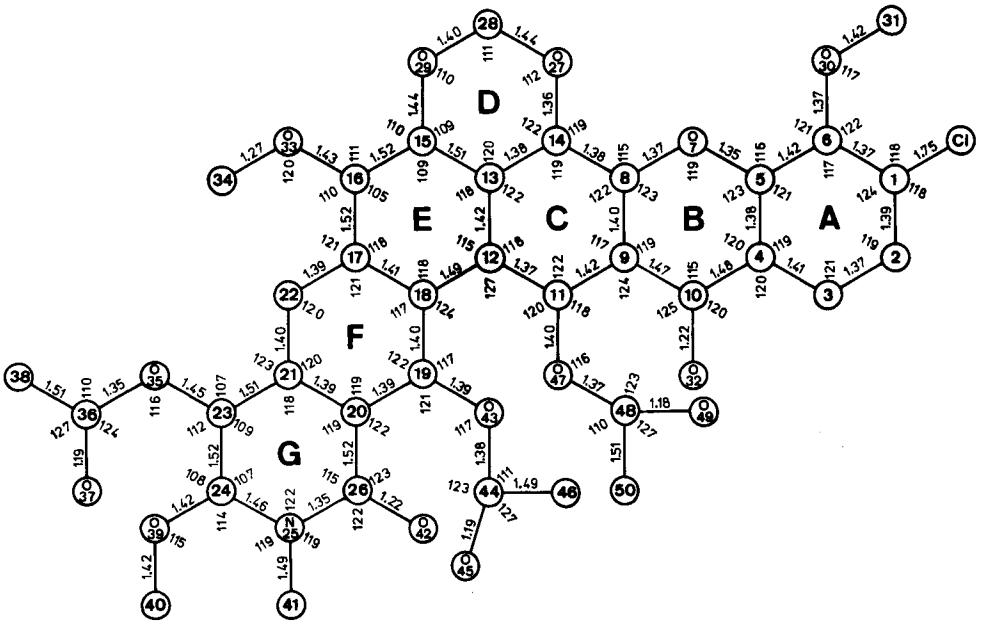


Fig. 2. *Molecular geometry.* Bond lengths (in Å) and bond angles (in degrees).

corresponding standard deviations for C–C, C–N and C–O bonds are between 0.005 and 0.011 Å (up to 0.018 Å for the included acetone), for bond angles between 0.5 and 0.8° (up to 1.2° for acetone)[2]).

Discussion. – The structural formulae (1) (R = H for free lysolipin I and R = $COCH_3$ for the triacetate) are in good agreement with the spectra of these compounds, which are given in Tables 3 and 4. Of particular interest are the acetyl signals in the ^{1}H-NMR. spectrum of the triacetate (Fig. 3). Instead of three discrete singlets of the acetyl groups there is a broad signal (integrating to 6 H atoms) overlapping with a sharp singlet (3H atoms), the latter being assigned to the acetyl group at O(35). The broad-

Table 3. *^{13}C-NMR. spectrum of lysolipin* (1) in *$CDCl_3$/DMSO* (TMS as internal standard)

No.	δ (ppm)	Multiplicity[a])	Assignments
1	181.26	*s*	C(10) (C=O, Xanthon)
2	168.26	*s*	C(26) (C=O, Amid)
3	158.60	*s*	C(1), C(5), C(6), C(8), C(11), C(14), C(19)
4	151.26	*s*	
5	149.65	*s*	
6	144.95	*s*	
7	143.17	*s*	
8	140.53	*s*	
9	138.86	*s*	
10	134.06	*s*	C(4), C(9), C(20)
11	133.09	*s*	
12	127.91	*s*	
13	125.48	*d*	C(2), C(3), C(22)
14	120.62	*d*	
17	116.15	*d*	
15	120.62	*s*	C(12), C(13), C(17), C(18), C(21)
16	117.77	*s*	
18	111.24	*s*	
19	110.37	*s*	
20	108.54	*s*	
21	92.63	*d*	C(24)
22	90.95	*t*	C(28)
23	78.87	*d*	C(16), C(23), C(24)
24	75.31	*d*	
25	67.70	*d*	
26	61.5	*q*	3 OCH_3
27	58.42	*q*	
28	57.65	*q*	
29	35.55	*q*	N–CH_3

[a]) Splitting under off-resonance conditions: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet

[2]) A table of observed structure amplitudes and of vibrational parameters is available on request.

Table 4. *^{1}H-NMR. spectra of lysolipin* (**1**, *R=H*) *and its triacetate* (**1**, *R=COCH$_3$*) *in CDCl$_3$* (100 MHz)

Free lysolipin (**1**, R = H)				Triacetate (**1**, R = $COCH_3$)				
(ppm)	m	J(Hz)	n	(ppm)	m	J(Hz)	n	Assignment[a])
				2.12	*s*		6	Acetone of crystallization[b])
				2.35	*s*		3	CH_3CO–O(35)
				2.35	br.		6	CH_3CO–O(43)
								CH_3CO–O(47)
2.65	br.		1					H–O(35)
3.37	*s*		6	3.32	*s*		3	CH_3–N(25)
				3.35	*s*		3	CH_3–O(33)
3.55	*s*		3	3.48	*s*		3	CH_3–O(39)
4.18	*s*		3	4.17	*s*		3	CH_3–O(30)
4.46	*d*	3.0	1[c])	4.54	*d*	2.3	1	H–C(15)
5.02	*d*	3.0	1[c])	4.93	*d*	2.3	1	H–C(16)
4.70	*d*	4.1	1[c])	6.18	*d*	3.4	1	H–C(23)
5.03	?[d])		1[c])	4.99	*b*[d])		1	H–C(24)
5.40	*d*	5.7	1	5.43	*d*	5.7	1	H_2C(28)
5.63	*d*	5.7	1	5.70	*d*	5.7	1	
7.09	*s*		1	7.22	*s*		1	H–C(22)
7.37	*d*	8.0	1	7.34	*d*	8.0	1	H–C(2)
7.94	*d*	8.0	1	7.88	*d*	8.0	1	H–C(3)
12.93	*s*		1					H–O(43)
13.10	*s*		1					H–O(47)

[a]) In order to avoid confusion the same numbering was used as for the crystal structure analysis.
[b]) This signal is absent in the spectrum of an amorphous sample prepared by precipitation from chloroform with diethyl ether.
[c]) Irradiation at 5.03 ppm transformed both doublets at 4.46 and 4.70 to singlets.
[d]) The shape of this signal is not clear because of overlapping with the signal of H–C(16).

ening of the signals of the acetyl groups 43 and 47 can be attributed to a partial hindrance of free rotation around the CH_3–CO bonds. This is supported by the crystal structure (see Fig. 4). The shortest contact between H atoms is 3.27 Å (H(461) ... H(502)) and between H and C or O atoms 2.28 Å (H(502) ... O(45)). The difficult formation of the acetyl derivative [2] is also compatible with steric hindrance at these two centres.

Only two antibiotics of a similar polycyclic xanthone structure are described in the literature, albofungin (kanchanomycin) and chloroalbofungin [4]. The xanthone ring of lysolipin is in an inverted arrangement with respect to these, and the hydrazino group occurring in albofungin is replaced here by a N–CH_3 group.

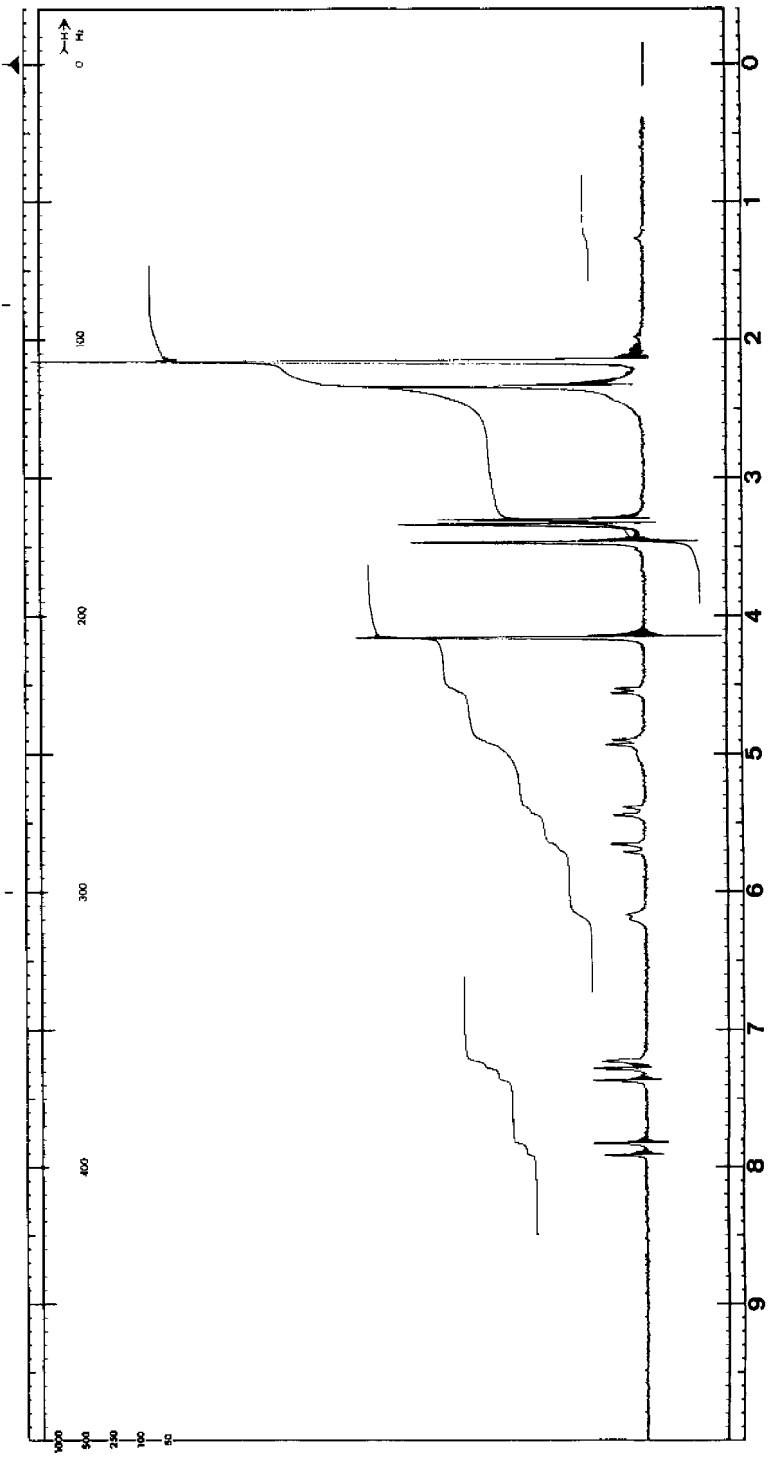


Fig. 3. ^{1}H-NMR. spectrum of lysolipin triacetate (**1**, R = $COCH_3$) acetone solvate in $CDCl_3$ (100 MHz)

A stereo-view of the lysolipin triacetate molecule is depicted in Fig. 4. Rings A, B, C are aromatic and planar. The mean deviation of the 14 atoms from their best plane is 0.038 Å with a maximum of 0.08 Å for C(13). However, some of the atoms attached to this system show marked deviations from the plane: C(15), 0.38 Å; O(27), 0.20 Å; O(30), 0.13 Å and O(32), 0.10 Å. The aromatic ring F is planar within 0.045 Å, with similar deviations of attached atoms: C(16), 0.25 Å; C(26), 0.18 Å; O(43), 0.17 Å and C(23), 0.14 Å. Some of the side group atoms show quite considerable anisotropic temperature factors, *e.g.* Cl and C(34).

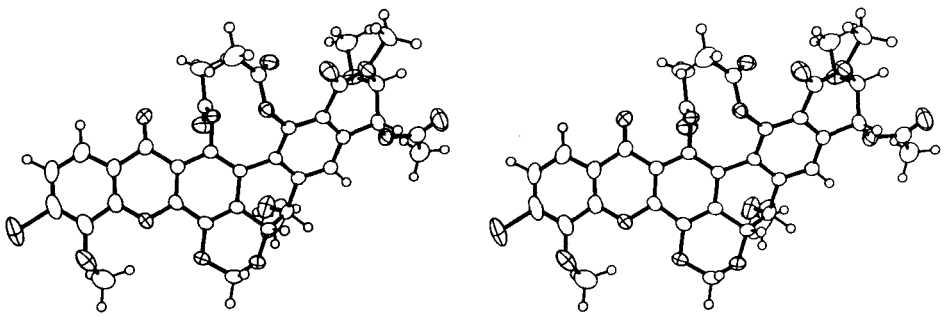


Fig. 4. *Stereoscopic view of lysolipin triacetate* (**1**, R = $COCH_3$)

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