Table 3. *Twist and out-of-plane bending parameters* (°) *describing the amide groups* (*Warshel, Levitt & Lifson, 1970; Winkler & Dunitz, 1971*)

Amide group	τ'	χ_C	χ_N
C2—N18	0·1 (5)	0·9 (5)	39·6 (5)
C13—N12	−0·1 (4)	−2·5 (4)	43·6 (4)
C7—N6	−11·2 (5)	−1·1 (4)	51·5 (5)

given. The non-planar bond arrangement at N (χ_N) is common for the three amide groups as well as the nearly planar arrangement at carbonyl C (χ_C). The torsion (τ') around the CO—N peptide bond is significant for the third amide group which also has a pronouncedly higher pyramidity at N. The significant difference of this amide group is also visible in bond lengths and angles. A superposition of the Aze residues, excluding H atoms, also shows that only two of the residues are comparable. The angles between LS-weighted planes of the amide groups 1, 2, 3 are 1–2: 125 (1)°; 1–3: 133 (1)°; and 2–3: 126 (1)°. The shorter C7—O8 carbonyl bond length and the longer C7—N6 peptide bond length are probably correlated with extremely high non-planarity at N6 (χ_N).

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Structure and Conformation of 3'-*O*-Acetyl-2'-deoxy-5-methoxymethyluridine

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Abstract. $C_{13}H_{18}N_2O_7$, $M_r = 314\cdot297$, triclinic, $P1$, $a = 6\cdot0321$ (4), $b = 6\cdot775$ (5), $c = 9\cdot6699$ (7) Å, $\alpha = 76\cdot917$ (6), $\beta = 78\cdot871$ (6), $\gamma = 75\cdot344$ (6)°, $V = 368\cdot54$ Å^3, $Z = 1$, $D_m = 1\cdot43$, $D_x = 1\cdot416$ g cm^{-3}, Cu $K\alpha$ radiation (Ni filtered), $\lambda = 1\cdot5418$ Å, $F(000) = 166$, $T = 287$ K, final conventional R factor $= 0\cdot034$, $wR = 0\cdot044$ for 1359 reflections and 268 variables. The structure was solved using the *XTAL* system. The conformation of the furanose ring is best described as intermediate between ^2E and ^2_1T; the pseudorotational parameters are $P = 148\cdot9°$ and $\tau_m = 33\cdot4°$. The CH$_2$OH, C(5'), side chain has the g^+ conformation, the

carbonyl bond of the 3'-acetoxy group is *syn* to the C(3')—O(3',1) bond on the sugar ring and the glycosidic bond conformation is *anti* [$\chi = -137\cdot6$ (3)°]. The methoxy group of the 5-methoxymethyl substituent is on the same side of the pyrimidine plane as O(4') of the furanose ring. Comparison with 2'-deoxy-5-methoxymethyluridine shows that intermolecular attractions have little effect on the internal conformations of the molecule in the solid state.

Introduction. The marginal efficacy of antiviral drugs in topical treatment of herpes simplex virus infections is due to poor penetration into the cells of the epidermis where virus replication is occurring (Richards, Kern, Overall & Glasgow, 1982). This limitation can be overcome by utilizing pro-drug derivatives with greater

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lipophilicity. For example, the efficacy of the antiviral agent 9-β-D-arabinofuranosyladenine can be significantly increased by the use of its acetyl derivative (Shannon, Arnett, Baker, Kumar & Higuchi, 1983; Shannon et al., 1985). In this paper, we describe the crystal structure of 3'-O-acetyl-2'-deoxy-5-methoxymethyluridine (MMAcdUrd) which can serve as a pro-drug for the antiviral agent 2'-deoxy-5-methoxymethyluridine (MMdUrd), a selective antiherpes agent (Ayisi, Gupta, Meldrum, Taneja & Babiuk, 1980; Ayisi, Gupta & Babiuk, 1985; Gupta, 1980). This investigation is part of a series of conformational studies undertaken to determine the effect of changes in structure on antiviral activity (El-Kabbani, Ekiel, Delbaere, Tourigny, Stuart & Gupta, 1986; Quail, Ekiel, El-Kabbani, Tourigny, Delbaere, Stuart & Gupta, 1986; Gupta, Tourigny, Stuart, DeClercq, Quail, Ekiel, El-Kabbani & Delbaere, 1987). In this paper the crystal structure of a 3'-ester of a deoxyribonucleoside in which intermolecular hydrogen bonding involving the 3'-OH group is not possible is discussed.

Experimental. The title compound was prepared as follows. 2'-Deoxy-5-methoxymethyl-5'-O-triphenylmethyluridine (2 mmol, 1·18 g), prepared by the procedure of Stuart, Ayisi, Tourigny & Gupta (1985), was dissolved in 11 ml of anhydrous pyridine and 3 ml (32 mmol) of acetic anhydride was added. The solution was stirred for 20 h at 293 K and then added dropwise into 40 volumes of ice-cold water. The precipitate was recovered by filtration, dissolved in 20 ml of CHCl$_3$ and washed successively with 0·1 M HCl, 5% NaHCO$_3$ and H$_2$O. The solvent was removed in vacuo and detritylation was accomplished using 10 ml of 80% HOAc at 323 K for 4 h. After chilling at 277 K, the precipitate (triphenylmethanol) was removed by filtration. The solvent was removed in vacuo and the oil was co-evaporated three times with absolute ethanol to remove the last traces of water. The residue was dissolved in a minimal amount of CCl$_4$ and applied to a silica gel column (2·5 × 95 cm) which was previously equilibrated with CCl$_4$. The product was eluted with CCl$_4$–EtOAc (15:85). Crystallization from EtOAc–petroleum ether (80–100°C) gave MMAcdUrd (391 mg, yield 62%), m.p. 378–380 K, UV (CH$_3$OH), λ_{max} 263 nm (ε 9,860), λ_{min} 232 nm (ε 1,920), NMR (Me$_2$SO-d_6), δ 7·91 (s, 1, 6-H), 6·14 (t, 1, 1'-H), 5·19 (broad, 1, 5'-OH), 4·01 (s, 2, 5-CH$_2$OCH$_3$), 3·96 (m, 1, 3'-H), 3·60 (d, 2, 5'-H), 3·42 (m, 1, 4'-H), 3·20 (s, 3, 5-CH$_2$OCH$_3$), 2·25 (m, 2, 2'2''-H), and 2·02 (s, 3, 3'-CH$_3$CO). Analysis: calc. for C$_{13}$H$_{18}$N$_2$O$_7$: C, 49·68; H, 5·77; N, 8·91%; found: C, 49·55; H, 6·15; N, 9·00%.

For X-ray analysis, crystals of MMAcdUrd were grown from a supersaturated solution of EtOAc at 295 K over a period of two weeks. Quantitative data

collection was on an Enraf–Nonius CAD-4F diffractometer with an $\omega/2\theta$ scan. The crystal was 0·12 × 0·075 × 0·12 mm in size and exhibited the forms {100}, {$\bar{1}$00}, {010}, {0$\bar{1}$0}, {001}, and {00$\bar{1}$}; accurate cell parameters refined from setting angles of 25 reflections with $29 \le 2\theta \le 59°$; max. $(\sin\theta)/\lambda = 0·6092$ Å^{-1}; $-7 \le h \le 7$, $-8 \le k \le 8$, $0 \le l \le 11$; three reflections used for intensity and centering standards [016, $\bar{1}$31, 313]; 1659 reflections collected, 1359 unique reflections measured, 46 unobserved reflections [$I < 2\sigma(I)$]; no absorption correction. Scattering factors from International Tables for X-ray Crystallography (1974). The merging R was 0·020 for 346 replicate reflections. The intensities were corrected for drift (largest correction = 0·878) and for Lorentz and polarization effects.

X-ray diffraction data collected on the MMAcdUrd crystal were processed using the XTAL system (Stewart & Hall, 1983). The structure was solved using the structure solution part of the XTAL system. The figures of merit CFOM and AMOS were used to choose the best set of phases used in the structure determination. The values for CFOM and AMOS used for structure solution were 0·53 and 95%, respectively. The positions of 21 of the non-H atoms were determined from a calculated E map. The remaining non-H atom was found in a difference Fourier map. Least-squares isotropic refinement gave an R value of 0·119. Anisotropic refinement was then carried out and gave an R value of 0·074. The positions of the H atoms were located by using difference Fourier maps. Finally, full-matrix least-squares refinement on F of anisotropic temperature factors for the non-H atoms and isotropic refinement for the H atoms converged to $R = 0·034$ and $wR = 0·044$, for 1359 reflections and 268 variables using $w = 1/[\sigma^2(F)]$ with a maximum shift/e.s.d. = 0·276. The average shift/e.s.d. ratio was 0·0401. $S = 2·535$; $(\Delta\rho)_{max} = 0·292$ and $(\Delta\rho)_{min} = -0·363$ e Å^{-3} on the final difference Fourier map. An ORTEP (Johnson, 1965) representation of the molecule is shown in Fig. 1 and final atomic coordinates are given in Table 1.* A VAX8600 computer at the University of Saskatchewan was used to carry out all crystallographic computations.

Discussion. The glycosyl bond has the anti conformation, the 5'-CH$_2$OH side chain has the g^+ conformation, the carbonyl of the 3'-acetoxy group is syn to the sugar ring, and the methoxy group of the 5-methoxymethyl side chain is on the same side of the

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Table 1. *Positional parameters and average temperature factors* ($Å^2$) *with e.s.d.'s in parentheses*

$$U_{eq} = (U_{11} + U_{22} + U_{33})/3.$$

	x	y	z	$U_{eq} \times 10^3$
N(1)	0·43462	0·67838	0·32312	32
C(2)	0·3222 (6)	0·8669 (5)	0·3601 (4)	32
O(2)	0·3764 (5)	1·0307 (4)	0·2993 (3)	45
N(3)	0·1474 (6)	0·8576 (5)	0·4729 (4)	35
C(4)	0·0805 (6)	0·6832 (5)	0·5570 (4)	35
O(4)	−0·0783 (6)	0·6992 (5)	0·6566 (4)	52
C(5)	0·2176 (6)	0·4883 (5)	0·5178 (4)	33
C(5,1)	0·1731 (6)	0·2866 (5)	0·6063 (4)	37
O(5,2)	−0·0277 (5)	0·2376 (4)	0·5766 (3)	40
C(5,3)	−0·2134 (8)	0·2360 (9)	0·6901 (5)	66
C(6)	0·3833 (6)	0·4955 (5)	0·4043 (4)	33
C(1')	0·6280 (6)	0·6705 (5)	0·2037 (3)	32
C(2')	0·8638 (6)	0·5848 (5)	0·2522 (4)	34
C(3')	1·0056 (6)	0·4906 (5)	0·1267 (4)	33
O(3',1)	1·1007 (5)	0·6550 (4)	0·0286 (3)	36
C(3',2)	1·2653 (6)	0·5955 (6)	−0·0783 (4)	39
O(3',3)	1·3230 (5)	0·4201 (5)	−0·0978 (4)	51
C(3',3)	1·3598 (8)	0·7753 (8)	−0·1677 (5)	55
C(4')	0·8278 (6)	0·4285 (5)	0·0601 (4)	34
O(4')	0·6028 (5)	0·5326 (5)	0·1214 (3)	39
C(5')	0·8381 (7)	0·1978 (6)	0·0901 (4)	49
O(5')	0·8182 (6)	0·1150 (5)	0·2401 (4)	57

Table 2. *Bond lengths* (Å) *and bond angles* (°) *with e.s.d.'s in parentheses*

N(1)—C(2)	1·376 (3)	C(1')—C(2')	1·515 (5)
N(1)—C(6)	1·381 (3)	C(1')—O(4')	1·409 (5)
N(1)—C(1')	1·474 (3)	C(2')—C(3')	1·512 (5)
C(2)—O(2)	1·224 (4)	C(3')—O(3',1)	1·451 (4)
C(2)—N(3)	1·365 (4)	C(3')—C(4')	1·536 (6)
N(3)—C(4)	1·379 (5)	O(3',1)—C(3',2)	1·344 (4)
C(4)—O(4)	1·223 (4)	C(3',2)—O(3',3)	1·198 (5)
C(4)—C(5)	1·458 (5)	C(3',2)—C(3',3)	1·497 (6)
C(5)—C(5,1)	1·497 (5)	C(4')—O(4')	1·444 (4)
C(5)—C(6)	1·335 (4)	C(4')—C(5')	1·512 (5)
C(5,1)—O(5,2)	1·429 (6)	C(5')—O(5')	1·425 (5)
O(5,2)—C(5,3)	1·409 (5)		

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C(2)—N(1)—C(6)	121·0 (2)	N(1)—C(1')—C(2')	113·6 (2)
C(2)—N(1)—C(1')	119·3 (2)	N(1)—C(1')—O(4')	107·5 (3)
C(6)—N(1)—C(1')	119·5 (2)	C(2')—C(1')—O(4')	106·0 (3)
N(1)—C(2)—O(2)	123·1 (3)	C(1')—C(2')—C(3')	102·6 (3)
N(1)—C(2)—N(3)	114·8 (3)	C(2')—C(3')—O(3',1)	106·4 (3)
O(2)—C(2)—N(3)	122·0 (3)	C(2')—C(3')—C(4')	104·1 (3)
C(2)—N(3)—C(4)	127·8 (3)	O(3',1)—C(3')—C(4')	110·6 (3)
N(3)—C(4)—O(4)	120·4 (3)	C(3')—O(3',1)—C(3',2)	115·9 (3)
N(3)—C(4)—C(5)	114·2 (3)	O(3',1)—C(3',2)—O(3',3)	122·9 (3)
O(4)—C(4)—C(5)	125·3 (3)	O(3',1)—C(3',2)—C(3',3)	111·3 (3)
C(4)—C(5)—C(5,1)	119·7 (3)	O(3',3)—C(3',2)—C(3',3)	125·8 (3)
C(4)—C(5)—C(6)	118·5 (3)	C(3')—C(4')—O(4')	106·2 (3)
C(5,1)—C(5)—C(6)	121·8 (3)	C(3')—C(4')—C(5')	114·3 (3)
C(5)—C(5,1)—O(5,2)	112·3 (3)	O(4')—C(4')—C(5')	108·7 (3)
C(5,1)—O(5,2)—C(5,3)	115·5 (4)	C(1')—O(4')—C(4')	109·9 (3)
N(1)—C(6)—C(5)	123·4 (3)	C(4')—C(5')—O(5')	111·5 (4)
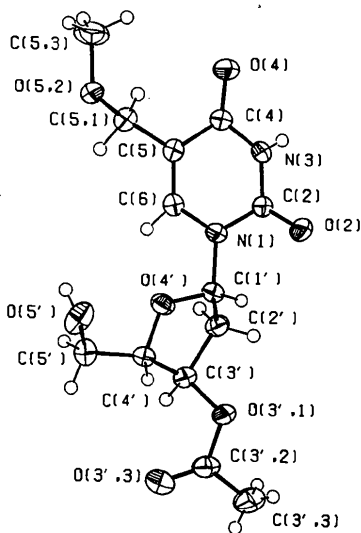
Fig. 1. *ORTEP* (Johnson, 1965) diagram and atomic numbering for 3'-O-acetyl-2'-deoxy-5-methoxymethyluridine.

Table 3. *Comparison of selected torsion angles* (°) *with e.s.d.'s in parentheses*

	MMAcdUrd	MMdUrd*
C(1')—C(2')—C(3')—C(4')	−28·6 (3)	−36·0
C(2')—C(3')—C(4')—O(4')	14·2 (3)	22·4
C(3')—C(4')—O(4')—C(1')	7·3 (3)	1·4
C(4')—O(4')—C(1')—C(2')	−26·0 (3)	−24·8
O(4')—C(1')—C(2')—C(3')	33·9 (3)	38·0
O(5')—C(5')—C(4')—O(4')	−63·8 (4)	−63·1
C(2)—N(1)—C(1')—O(4')	−137·6 (3)	−126·7
C(5)—C(5,1)—O(5,2)—C(5,3)	−113·9 (4)	−114·2
C(6)—C(5)—C(5,1)—O(5,2)	−103·4 (4)	−99·2
C(3')—O(3',1)—C(3',2)—C(3',3)	−176·8 (3)	—
C(3')—O(3',1)—C(3',2)—O(3',3)	4·0 (6)	—
C(4')—C(3')—O(3',1)—C(3',2)	−78·8 (4)	—
H(1')—C(1')—C(2')—H(2',1)	32 (3)	36
H(1')—C(1')—C(2')—H(2',2)	156 (3)	162
H(2',1)—C(2')—C(3')—H(3')	86 (3)	82
H(2',2)—C(2')—C(3')—H(3')	−34 (4)	−41
H(3')—C(3')—C(4')—H(4')	−102 (3)	−97
H(4')—C(4')—C(5')—H(5',1)	65 (4)	60
H(4')—C(4')—C(5')—H(5',2)	−49 (3)	−62

* The data for the parent compound, MMdUrd, are included for comparison (El-Kabbani, Ekiel, Delbaere, Tourigny, Stuart & Gupta, 1986).

pyrimidine plane as O(4') of the furanose ring. Bond lengths and angles for MMAcdUrd are given in Table 2. They are in agreement with the values reported for MMdUrd (El-Kabbani *et al.*, 1986). The mean of the absolute differences between the lengths of corresponding bonds in the two molecules is 0·010 ± 0·006 Å and the mean of the absolute differences between corresponding bond angles is 0·73 ± 0·58°. A comparison of selected torsion angles for MMAcdUrd

and MMdUrd is shown in Table 3. The deoxyribose ring has an envelope conformation in MMAcdUrd with C(2')-*endo* and 0·50 Å from the plane of the other four atoms (planar within 0·044 Å). A pseudorotational analysis of the furanose-ring torsional angles in terms of the two degrees of freedom for ring puckering (Altona & Sundaralingam, 1972) gives a phase angle *P*

Table 4. *Comparison of MMAcdUrd and MMdUrd distances between equivalent atoms when the pyrimidine ring of MMAcdUrd is superimposed on the pyrimidine ring of MMdUrd*

MMAcdUrd–MMdUrd	Distance (Å)	MMAcdUrd–MMdUrd	Distance (Å)
N(1)···N(1)	0·018	C(6)···C(6)	0·016
C(2)···C(2)	0·037	C(1')···C(1')	0·109
O(2)···O(2)	0·101	C(2')···C(2')	0·135
N(3)···N(3)	0·016	C(3')···C(3')	0·260
C(4)···C(4)	0·041	O(3')···O(3',1)	0·373
O(4)···O(4)	0·104	C(4')···C(4')	0·249
C(5)···C(5)	0·013	O(4')···O(4')	0·158
C(5,1)···C(5,1)	0·112	C(5')···C(5')	0·322
O(5,2)···O(5,2)	0·518	O(5')···O(5')	0·281
C(5,3)···C(5,3)	1·581		

Fig. 3. Stereoscopic view of the packing of MMAcdUrd in the unit cell.
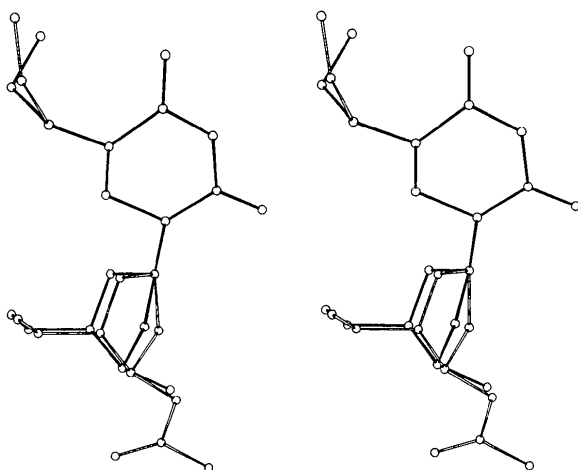

Fig. 2. Stereoscopic view of the superimposed molecules MMdUrd (solid bonds) and MMAcdUrd (open bonds). H atoms are not shown for the sake of clarity.

$=148\cdot9°$ and a puckering amplitude $\tau_m=33\cdot4°$ suggesting that esterification of the 3'-OH group results in a slight distortion of the envelope ^2E conformation towards the twist ^2_1T conformation. There is also a small change in the glycosidic torsion angle, C(2)—N(1)—C(1')—O(4'), from $-126\cdot7$ to $-137\cdot6°$. The carbonyl bond of the acetyl group is *syn* to the C(3')—O(3',1) bond on the sugar ring. A similar conformation for 3'-O-acetyl-2'-deoxy-4-thiothymidine has been reported (Saenger & Suck, 1971). However, there is very little change in the conformation of the other side chains as expressed in the O(5')—C(5')—C(4')—O(4'), C(5)—C(5,1)—O(5,2)—C(5,3), and C(6)—C(5)—C(5,1)—O(5,2) torsion angles (Table 3).

The two molecules were compared using the computer program *PROFIT* (Smith, 1983). The planar pyrimidine ring of MMAcdUrd was superimposed on
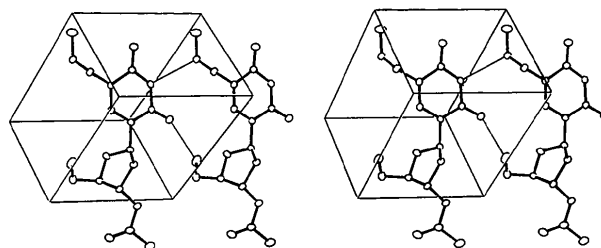
that of MMdUrd and the distances between equivalent atoms in each molecule were calculated (Table 4). The average distance between equivalent atoms is $0\cdot23$ Å. A stereoscopic view of the two superimposed molecules is shown in Fig. 2.

A stereoscopic view of the packing of MMAcdUrd in the unit cell is shown in Fig. 3. There are two intermolecular hydrogen bonds per unit cell. The first is N(3)—H···O(5,2); the distances from O(5,2) to N(3) and H are $2\cdot85$ (1) and $2\cdot15$ (5) Å, respectively; the angle N(3)—H···O(5,2) is 161 (5)°. The second is O(5')—H···O(2); the distances from O(2) to O(5') and H are $2\cdot79$ (1) and $1\cdot95$ (6) Å, respectively; the angle O(5')—H···O(2) is 174 (6)°. In contrast, hydrogen bonding in MMdUrd does not involve N(3)H nor O(5')H but rather O(4) with O(3')H of a second molecule and O(5,2) with O(3')H of a third molecule (El-Kabbani *et al.*, 1986). It is interesting to note that the lack of O(3')H-bonding in MMAcdUrd ($P1$) results in a change in the crystal structure compared to MMdUrd ($P2_12_12_1$) but there is very little change in the intramolecular conformation. Preliminary studies indicate that the 3'-acetate derivative retains the antiviral activity of the parent compound. The thermodynamically more stable conformation of the nucleoside observed in the crystalline state may be useful in predicting antiviral activity.

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# Isodrimenin, (5aα,9aβ)-4,5,5a,6,7,8,9,9a-Octahydro-6,6,9a-trimethylnaphtho[1,2-c]furan-1(3H)-one

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Abstract. $C_{15}H_{22}O_2$, $M_r = 234.34$, orthorhombic, $P2_12_12_1$, $a = 7.825$ (1), $b = 23.669$ (2), $c = 7.259$ (1) Å, $V = 1344.5$ (1) Å^3, $Z = 4$, $D_m = 1.10$ (1), $D_x = 1.157$ Mg m^{-3}, $\lambda(\text{Cu }K\alpha) = 1.54178$ Å, $\mu = 0.595$ mm^{-1}, $F(000) = 512$, $T = 269$ K, $R = 0.046$ for 1274 unique observed reflections with $I > 2\sigma(I)$. The molecule of this naturally occurring lactone exhibits a cyclohexane ring (chair) *trans* fused to a cyclohexene ring, with a five-membered lactone ring (planar) also fused to the cyclohexene ring. The structure consists of discrete molecules.

Introduction. The purpose in undertaking the structural analysis of natural isodrimenin (I) was to check the behavior of the two axial methyl groups on the cyclohexane ring, also present in drimenol. In the structure determination of the latter (Escobar & Wittke, 1984), the methyl H atoms were not resolved and the methyl C atoms exhibit a separation shorter than the normal van der Waals distance. Isodrimenin, like drimenol, was isolated from the bark of the Chilean canelo tree (*Drymis winteri* Forst). Its constitution and stereochemistry (I) were determined by chemical and spectroscopic methods (Appel, Connolly, Overton & Bond, 1960). Several total syntheses of this lactone and the isomeric drimenin, also naturally occurring, have been reported (Liapis, Ragoussis & Ragoussis, 1985)

and they have been used to prepare more biologically active members of the drimane class, such as warburganal.
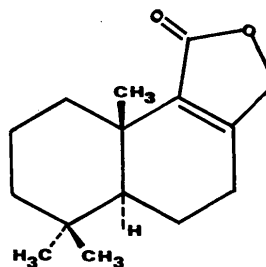
(I)

Experimental. Colorless prismatic crystals, D_m measured with pycnometer and water; single crystal $0.29 \times 0.53 \times 0.06$ mm used for X-ray analysis, Philips PW 1100 computer-controlled four-circle diffractometer, graphite monochromator, Cu $K\alpha$ radiation, $\omega/2\theta$ scan; cell parameters from least-squares refinement of setting angles of 66 strong reflections ($11.9 \le 2\theta \le 85.5°$); two standard reflections (022, 02$\bar{2}$) every 76 measurements showed monotonic decay of intensity (total decay 2.6%), correction applied; 2770 *hkl* and $\bar{h}\bar{k}\bar{l}$ ($|h|0/9$, $|k|0/27$, $|l|0/27$) up to $(\sin\theta)/\lambda = 0.59$ Å^{-1}, 1358 unique ($R_{\text{int}} = 0.009$), 84