Methylation of Hallerin: Conformational Aspects from *X*-Ray Analysis† and MO Calculations

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The stereochemistry at the ketal centre of methylhallerin‡ (**6**) has been established by *X*-ray analysis. The stereochemical outcome of the methylation of hallerin and of pairs of related anomeric sesquiterpene lactols has been studied by means of geometrical and theoretical calculations (MNDO method). Model lactols and methyl lactols were chosen with conformational features simulating the effects of the presence of the ten-membered ring in as found in (**6**) the solid state. The results showed that neither thermodynamic nor steric effects alone can explain the fact that exclusively one methyl derivative is obtained upon alkylation of the pairs of anomeric lactols with CH_3I–Ag_2O. However, the anomeric lactols investigated show a difference in accessibility towards methylation, which, although not relevant in solution, might play an important role when the molecule is adsorbed on the surface of Ag_2O, where the alkylation reaction is expected to take place.

In the course of studies on naturally occurring sesquiterpene lactols, it was noticed that the more acidic hemiacetal hydroxy group can be chemoselectively alkylated in the presence of alcohol functions by treatment with methyl iodide and silver(I) oxide in dry dichloromethane.[1-3]

In general, when the starting lactol exists in one anomeric form only, methylation occurs with retention of configuration at the anomeric centre.[1,2] However, from compounds (**1a,b**)—(**5a,b**), all existing in solution as almost equimolecular mixtures of anomers, only one methyl derivative was obtained in each case, thus showing that equilibration at the anomeric centre takes place during the reaction.[3]

Spectral data suggested that in methylhallerin‡ (**6**) the acetal methoxy group is β-oriented and *trans* to the vicinal methyl group; chemical correlation with (**6**) established that the configuration at C(12) is the same in the methyl acetals obtained from the other pairs of lactols investigated.[3]

It is known that in the mixtures obtained from methylation of sugars, furanosides in which O(1) is *trans* to O(2) prevail,[4] and a methyl group would be expected to exert a greater steric effect than an oxygen function. However, the exclusive production of one methyl derivative from the pairs of anomeric lactols (**1a,b**)—(**5a,b**) is still somewhat surprising.

Methylation of C(8)-closed lactols such as hallerol, which exist in solution in one anomeric form only, yielded, under the same conditions, exclusively the methyl derivative in which the methoxy group at C(12) and the methyl at C(11) are *cis*.[1,3] Furthermore, equilibration at the anomeric centres of the lactols (**2a,b**)—(**4a,b**) under basic conditions, gave *C*(8)-deacyl derivatives with anomeric composition similar to that of the starting material, suggesting that the two anomeric forms have similar energy contents. Not even from models can a particular preference for β- over α-alkylation be inferred.

An *X*-ray diffraction study of the methyl derivative of hallerin, (**6**), was carried out. The experimental conformation found in the solid state was used to generate simplified models of lactols and methyl lactols, on which theoretical calculations were carried out to investigate the stereochemical aspects of the methylation reaction.

Table 1. Atom co-ordinates (× 10^4) and temperature factors (Å^2 × 10^3)

Atom	*x*	*y*	*z*	U_{iso}[a]
O(1)	4 824(5)	−2 499(3)	1 467(1)	80(1)
O(2)	4 709(5)	−1 150(3)	759(1)	80(1)
O(3)	1 003(4)	−10(2)	1 011(1)	49(1)
O(4)	2 579(5)	1 677(3)	1 071(1)	85(1)
C(1)	1 948(6)	371(4)	2 828(2)	55(2)
C(2)	2 811(6)	−38(4)	3 346(2)	62(2)
C(3)	4 585(7)	−720(4)	3 220(2)	66(2)
C(4)	4 213(6)	−1 736(3)	2 839(2)	50(1)
C(5)	4 185(6)	−1 525(3)	2 310(2)	50(1)
C(6)	3 433(6)	−2 259(3)	1 864(2)	54(1)
C(7)	1 806(6)	−1 750(3)	1 544(2)	47(1)
C(8)	1 656(6)	−380(3)	1 538(1)	46(1)
C(9)	346(6)	146(4)	1 955(2)	60(2)
C(10)	697(6)	−194(3)	2 542(2)	50(1)
C(11)	2 135(6)	−2 310(3)	978(2)	56(2)
C(12)	4 175(7)	−2 272(4)	943(2)	65(2)
C(13)	1 424(9)	−3 572(4)	956(2)	89(2)
C(14)	−369(7)	−1 226(4)	2 758(2)	70(2)
C(15)	3 689(7)	−2 869(4)	3 105(2)	66(2)
C(16)	1 612(6)	1 021(3)	812(2)	53(1)
C(17)	955(6)	1 226(4)	248(2)	56(2)
C(18)	574(7)	2 303(4)	83(2)	70(2)
C(19)	676(9)	3 438(4)	391(2)	89(2)
C(20)	797(7)	155(4)	−110(2)	73(2)
C(21)	6 609(9)	−978(7)	758(3)	129(3)

[a] Equivalent isotropic temperature factors defined as one third of the trace of the orthogonalised U_{ij} tensor.

Structural Study of Methylhallerin (**6**).—Table 1 lists the atomic parameters and Table 2 the bond distances and angles of non-hydrogen atoms, which are both within the ranges of values normally found in germacrane derivatives. Figure 1 shows a drawing of the molecule together with the atomic labelling.

† *Supplementary data* (see sections 5.6.3 of Instructions for Authors, in the January issue). H-Atom co-ordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

‡ (6*S*,7*R*,8*S*,11*S*,12*R*;1*E*,4*E*)-8-Angeloyloxy-6,12-epoxy-12-methoxygermacra-1(10),4-diene.

As suggested by n.m.r. spectroscopy, the $-OCH_3$ group at C(12) is β-oriented. The torsion angle sequence along the cyclodecadiene system (Table 3) shows that the ring adopts a chair-boat conformation, with the allylic methyl groups *syn* oriented on the α-face of the molecule. In terms of the conventions of Samek and Harmata,[5] the spatial arrangement of the double bonds can be referred to as $[_{15}D^5,^1D_{14}]$.

As expected, the values of some torsion angles differ considerably from those calculated for the chair-boat conformation of 1,5-dimethylcyclodeca-1,5-diene[6] [particularly those for C(6) and C(7) involved in the closure of the lactol ring].

The torsional strains associated with the out-of-plane bending of the substituents around the two double bonds are similar to each other, in contrast with the situation found in chair-chair germacradienes, where the double bond at C(4)–C(5) is generally more strained than the other.[7] In (**6**) both the proton and the oxygen atom at C(8) are involved in short intramolecular contacts, with H(5) and H(11), respectively [H(8) • • • H(5) 2.14 Å; O(3) • • • H(11) 2.34 Å]. Any attempt to

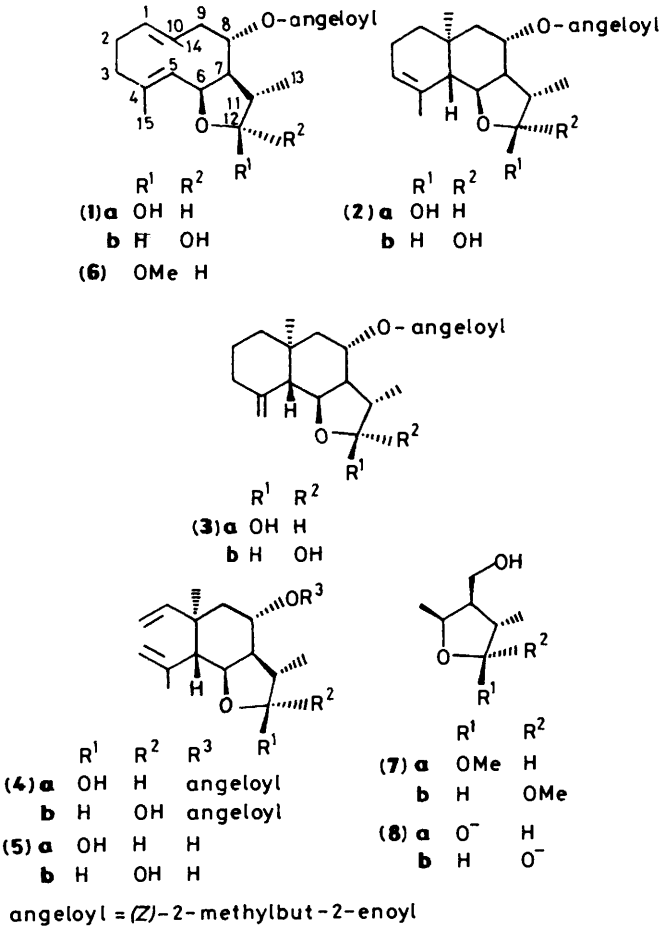

Table 2. Bond lengths (Å) and bond angles (°)

O(1)–C(6)	1.443(5)	O(1)–C(12)	1.400(5)
O(2)–C(12)	1.404(6)	O(2)–C(21)	1.415(7)
O(3)–C(8)	1.446(4)	O(3)–C(16)	1.342(4)
O(4)–C(16)	1.211(5)	C(1)–C(2)	1.498(6)
C(1)–C(10)	1.326(6)	C(2)–C(3)	1.551(7)
C(3)–C(4)	1.509(6)	C(4)–C(5)	1.324(5)
C(4)–C(15)	1.490(6)	C(5)–C(6)	1.484(5)
C(6)–C(7)	1.548(6)	C(7)–C(8)	1.554(5)
C(7)–C(11)	1.550(5)	C(8)–C(9)	1.531(6)
C(9)–C(10)	1.517(6)	C(10)–C(14)	1.506(6)
C(11)–C(12)	1.507(7)	C(11)–C(13)	1.522(6)
C(16)–C(17)	1.488(6)	C(17)–C(18)	1.315(6)
C(17)–C(20)	1.505(6)	C(18)–C(19)	1.494(6)
C(6)–O(1)–C(12)	110.3(3)	C(12)–O(2)–C(21)	113.7(4)
C(8)–O(3)–C(16)	117.9(3)	C(2)–C(1)–C(10)	126.9(4)
C(1)–C(2)–C(3)	110.0(3)	C(2)–C(3)–C(4)	110.6(4)
C(3)–C(4)–C(5)	118.5(3)	C(3)–C(4)–C(15)	115.4(3)
C(5)–C(4)–C(15)	125.7(4)	C(4)–C(5)–C(6)	129.2(4)
O(1)–C(6)–C(5)	109.9(3)	O(1)–C(6)–C(7)	106.0(3)
C(5)–C(6)–C(7)	117.3(3)	C(6)–C(7)–C(8)	115.5(3)
C(6)–C(7)–C(11)	100.7(3)	C(8)–C(7)–C(11)	114.2(3)
O(3)–C(8)–C(7)	108.7(3)	O(3)–C(8)–C(9)	106.2(3)
C(7)–C(8)–C(9)	115.2(3)	C(8)–C(9)–C(10)	115.6(3)
C(1)–C(10)–C(9)	120.3(4)	C(1)–C(10)–C(14)	123.2(4)
C(9)–C(10)–C(14)	116.4(3)	C(7)–C(11)–C(12)	101.3(3)
C(7)–C(11)–C(13)	111.2(3)	C(12)–C(11)–C(13)	111.6(4)
O(1)–C(12)–O(2)	111.6(4)	O(1)–C(12)–C(11)	106.5(4)
O(2)–C(12)–C(11)	108.9(4)	O(3)–C(16)–O(4)	122.6(4)
O(3)–C(16)–C(17)	111.5(3)	O(4)–C(16)–C(17)	125.9(4)
C(16)–C(17)–C(18)	120.2(4)	C(16)–C(17)–C(20)	116.5(3)
C(18)–C(17)–C(20)	123.2(4)	C(17)–C(18)–C(19)	128.9(4)

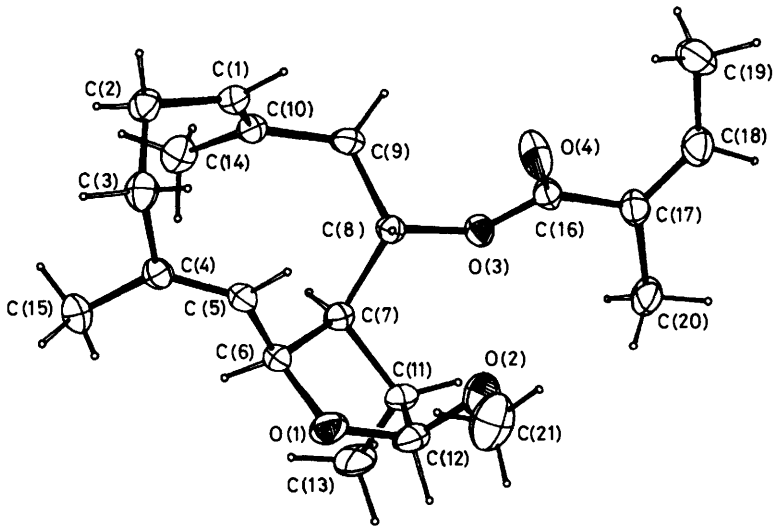

Figure 1. ORTEP II drawing of the molecule of methylhallerin (**6**) with the thermal ellipsoids at the 20% probability level

release one of these contacts by modification of the endocyclic torsion angles involving C(8) would shorten the other. The sesquiterpene lactone laserolide[8] has the same substitution pattern as (**6**) around the carbocycle, but differs in the five-membered ring. If laserolide adopted the same chair-boat conformation as (**6**) the presence of a β-CH_3 at C(11) would make the steric congestion around C(8) more marked. To avoid this, inversion of the torsion angle around C(6) and C(7) takes place.[8] In this way steric congestion around C(8) is decreased, but torsional strain around the C(4)=C(5) double bond is increased, resulting in a deviation from planarity of about 25°.

The ketalised γ-lactol ring adopts an envelope conformation, with C(11) as the flap at −0.60 Å from the mean plane through the remaining four atoms. The puckering parameters[9] are Φ_2 = 172.7(6)°, Q = 0.384(4) Å, and the asymmetry parameter[10] ΔC_s is 0.036(2) through C(11).

Theoretical Calculations.—Semiempirical molecular orbital calculations at the MNDO level,[11] using the standard program, were performed on models of methylhallerin, the epimeric methyl lactols (**7a** and **b**). The atomic labelling follows that adopted for methylhallerin except for the hydrogen bound to O(3), which has been indicated as H(30).

These models were chosen because the whole molecule was too large for the available computational facilities. On the other hand, the cyclodecadiene moiety of methylhallerin is rigid (with torsion angles in the solid state complying well with those found in solution by n.m.r.)[3] and models free of intramolecular short contacts involving both an α- and a β-oriented methoxy group at C(12) can be assembled. It was thus assumed that isomerisation at this centre had little if any effect on the geometry of the cyclodecadiene moiety.

In order to simulate the geometrical constraints imposed by the fusion of the γ-lactol ring to the cyclodecadiene moiety the following geometrical restrictions were adopted: the bond length C(8)–O(3), the bond angles centred at C(7), O(3), and C(6), and the torsion angles O(3)–C(8)–C(7)–C(6), H(30)–O(3)–C(8)–C(7), and C(5)–C(6)–C(7)–C(8) were kept fixed at the experimental (*X*-ray) values.

All other geometrical features of the models were optimised by using the standard Fletcher–Powell routine. The more relevant bond lengths, bond angles, and torsional angles are reported in Table 4, together with the corresponding experimental values.

The agreement in the geometrical features, including torsion angles, between (**6**) and the furanoid moiety of (**7a**) is generally good; the largest deviations involve the angles C(6)–O(1)–C(12)–C(11) and C(12)–O(1)–C(6)–C(7). This can be explained by an overestimation of non-bonded interactions from O(3) and O(2) atoms by MNDO.

The heats of formation are −557.936 and −557.112 kJ mol^{-1} for (**7a**) and (**7b**), respectively; the corresponding dipole moments are 1.131 and 1.962 D. The high selectivity of the methylation reaction cannot be explained in terms of the thermodynamic values, because the difference between the two isomers is less than 1 kJ mol^{-1} in favour of (**7a**). It is noteworthy that (**7a**), which corresponds to the only methyl acetal actually obtained from the anomeric mixture (**1a,b**), has an overall dipole moment smaller than that of (**7b**). However, it is difficult to estimate the role played in the stereochemical outcome of the reaction by these subtle electronic effects, which have been invoked to explain the so-called 'anomeric effect' observed in pyranosides.

The same calculations were also carried out on the anions (**8a** and **b**). Their heats of formation are −551.091 and −553.012 kJ mol^{-1}; again the difference is too small for any conclusion to be drawn.

In order to assess the accessibility of the O(2) site to a methyl group, two different approaches were followed. The first, a geometrical one, is based on the algorithm proposed by Gavezzotti[12] to compute the outer surface of any molecule. A computer program was developed (MOLC procedure), which allows one to evaluate the exposed surface of a given moiety, thus probing its ability to interact with a reactant (a similar approach can be found in ref.[13]). The results for the two isomers (**8a** and **b**) are similar, the percentage of exposed surface of O(2) being only 2% greater for the *trans*- than for the *cis*-isomer.

Table 3. Endocyclic torsion angles (°) of the germacradiene ring of methylhallerin

ω(1–2)	92.7	ω(6–7)	25.7
ω(2–3)	−56.1	ω(7–8)	−97.6
ω(3–4)	84.9	ω(8–9)	55.8
ω(4–5)	−163.4	ω(9–10)	81.7
ω(5–6)	115.0	ω(10–1)	−162.4

Table 4. Comparison between the geometrical parameters (bonds in Å; angles in degrees) computed for the model (**7a**) and the corresponding experimental values for (**6**)

Bond	*X*-Ray	MNDO	Bond	*X*-Ray	MNDO
C(6)–C(7)	1.548	1.583	C(7)–C(11)	1.549	1.569
C(11)–C(12)	1.507	1.586	C(12)–O(1)	1.400	1.412
C(6)–O(1)	1.443	1.403	C(12)–O(2)	1.404	1.400
O(2)–C(21)	1.415	1.398	C(11)–C(13)	1.522	1.539
C(7)–C(8)	1.554	1.565	O(3)–C(8)	1.446	1.377
C(5)–C(6)	1.484	1.546			

Angle	*X*-Ray	MNDO	Angle	*X*-Ray	MNDO
O(1)–C(6)–C(7)	106.0	107.9	C(6)–O(1)–C(12)–C(11)	−20.8	3.2
–C(11)	101.0	101.4	C(6)–O(1)–C(12)–O(2)	97.9	121.8
C(13)–C(11)–C(12)	112.0	113.0	C(11)–C(7)–C(6)–O(1)	26.0	25.5
C(7)–C(11)–C(12)	101.3	104.0	C(12)–C(11)–C(7)–C(6)	−36.9	−22.4
C(11)–C(12)–O(1)	107.1	107.3	C(12)–O(1)–C(6)–C(7)	−4.1	−18.6
C(12)–O(1)–C(6)	110.3	112.8	C(21)–O(2)–C(12)–C(11)	174.5	194.0
C(11)–C(7)–C(8)	114.2	116.8	C(7)–C(11)–C(12)–O(1)	36.5	13.5
O(2)–C(12)–C(11)	109.0	110.2			
C(21)–O(2)–C(12)	114.0	121.4			

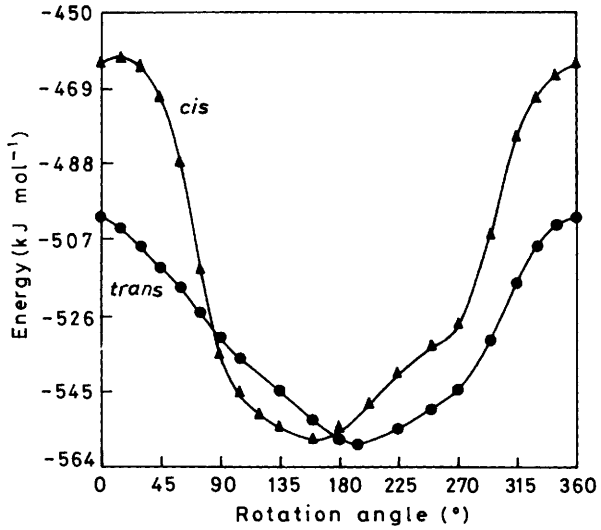

Figure 2. Energy profiles as a function of the torsion angle C(21)–O(2)–C(12)–C(11) for the two model isomers (**7a** and **b**)

The second approach was an energetic one: a conformational energy profile was calculated by rotating the methyl group around the C(12)–O(2) bond, allowing at the same time the optimisation of the C(12)–O(2)–C(21) angle to compensate for short non-bonded contacts. These calculations were intended to simulate the different energy conditions under which O(2) can be approached by the methylating agent.

The energy profile with respect to the torsion angle C(21)–O(2)–C(12)–C(11) is shown in Figure 2 for both isomers. Both curves display a rather flat minimum; the angular ranges within 20 kJ mol^{-1} from the absolute minimum are *ca.* 135° and *ca.* 175° for the *cis*- and *trans*-isomer, respectively. The most striking difference is with regard to the outer angular range, which is much steeper for (**7b**) owing to the presence of a *cis* vicinal methyl group. This, although not relevant in solution, might play an important role when the molecule is adsorbed on the surface of Ag_2O, where the reaction presumably takes place.[14]

In hallerin (**1a**,**b**), several possible binding sites with silver(I) oxide are present; it is however reasonable to postulate that, with regard to the lactol moiety, the interaction takes place on the front side [torsion angle around C(12)–O(2) in the range 90—270°], the back being snielded by the cyclodecadiene ring. This prevents approach of CH_3I from the front side, and makes attack at the hemiacetal hydroxy group possible only from the other side (torsion angle in the range 250—360°).

As Figure 2 shows, approach from this side is hindered in (**7b**), owing to the presence of the *cis* vicinal methyl, but still possible in (**7a**).*

The accessibility of the *cis*-isomer (**7b**) towards methylation might thus be drastically reduced after adsorption on the surface of silver oxide, where interconversion of the anomers can take place, owing to the alkaline nature of the latter. This might justify the exclusive formation of only one methyl acetal from each pair of lactols.

Experimental

X-Ray Analysis.—Diffraction data were collected with a Nicolet R3 diffractometer equipped with a graphite monochromator. The intensities were measured by ω-scan with variable speed; the cell parameters were obtained and refined from 25 reflections ($12° \leqslant 2\theta \leqslant 33°$). The intensities were corrected for background and Lorentz-polarisation effects,[15] but not for absorption. All subsequent calculations were carried out by the SHELXTL system.[16] The structure was solved by direct methods (RANTAN program[17]) and refined by full-matrix least-squares techniques with anisotropic temperature factors for non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and refined under geometrical constraints.

Crystal data. $C_{21}H_{32}O_4$, M = 348.5, orthorhombic, space group $P2_12_12_1$, a = 7.375(4), b = 11.316(8), c = 24.622(11) Å, Z = 4, D_c = 1.127 Mg m^{-3}, Mo-K_α radiation, λ = 0.710 69 Å, R = 0.047 for 1 243 observed intensities ($2° < \theta < 25°$) having $I > 2\sigma(I)$.

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* The interaction of the lactol moiety with silver oxide could involve both Ag^+ cations, through the geminal oxygen atoms, and the O^{2-} anions, through the acidic proton; the actual nature of the binding mode is largely undefined. Nevertheless an oversimplified model of the interaction was tested: an Li^+ ion was placed at a fixed distance of 2.2 Å from O(1) and O(2) on the plane through O(1)–C(12)–O(2) and the same conformational energy profile as already mentioned was calculated. The expected angular restrictions were observed. With respect to Figure 2, the differences between the two anomers are more marked: the difference in the absolute minimum is about 20 kJ mol^{-1} in favour of the *trans*-isomer, which displays a much wider energy profile. Of course these data are highly qualitative, owing to the nature of the approximations applied.