

The Structure of Hallerol, a Boat-Boat Germacrane Lactol

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The crystal and molecular structure of the *trans,trans*-germacradiene hallerol has been determined by direct methods from 1 118 unique intensities collected on a diffractometer and refined by least-squares methods to $R = 0.038$. The crystals are orthorhombic, space group $P2_12_12_1$, with $a = 6.010(1)$, $b = 11.846(3)$, $c = 20.035(5)$ Å. The cyclodeca-*trans-trans*-1(10),4-diene ring shows the boat-boat conformation with the double bonds in the parallel orientation; the methyl groups C(14) and C(15) are in the *anti*- β and α orientation respectively. This is the first case of such a configuration being found in the solid state. The α -methyl- γ -lactol is *trans*-fused at C(7)–C(8) and adopts an envelope conformation with C(12) above the plane of the other four atoms. The hydroxy lactol group acts as donor in an intramolecular hydrogen bond [with the hydroxy group at C(6) as acceptor] which plays an important role in stabilizing the energetically less favoured conformation of the cyclodecadiene ring of hallerol.

The conformation of germacra-1(10),4-dienes has been the subject of several investigations. In the case of the *trans,trans*-diastereoisomers four main conformations are possible (Figure 1). They are: the crossed (double-chair) [$^{15}D_5, ^1D_{14}$] and (chair-boat) [$^{15}D^5, ^1D_{14}$] conformations, typical of C(6) *trans*- and *cis*-germacrolides respectively, both in solution and in the solid state; the parallel [$^{15}D^5, ^1D_{14}$] and [$^{15}D_5, ^1D_{14}$] (both of the boat-boat type) which are instead characteristic of conformationally mobile compounds such as C(8)-*trans*-germacrolides, existing in solution as mixtures of interconverting crossed and parallel rotamers.¹

Whilst the [$^{15}D_5, ^1D_{14}$] conformation has been shown to be displayed in the solid state by some compounds,² the [$^{15}D^5, ^1D_{14}$] conformation is yet unreported even though variable-temperature n.m.r. studies suggest that the conformationally mobile germacrolide isabeline³ might exist as a rotamer of this kind. The present *X*-ray determination of the crystal structure of hallerol (1), a conformationally mobile sesquiterpene lactol (Figure 2), shows that it does exist in the solid state as a unique conformer of the [$^{15}D^5, ^1D_{14}$] type. Hallerol is the saponification product of hallerin,¹⁴ a mixture of anomeric sesquiterpene lactols isolated from the roots of the alpine plant *Laserpitium halleri* Crantz subsp. *halleri*.

Experimental

Crystal Data.— $C_{15}H_{24}O_3$, m.p. 482–483 K, orthorhombic, space group $P 2_12_12_1$, $a = 6.010(1)$, $b = 11.846(3)$, $c = 20.023(5)$ Å, $U = 1429.9(5)$ Å³, $Z = 4$, $D_c = 1.17$ Mg m⁻³, $F(000) = 552$, Mo- K_α radiation, $0.710 69$ Å, $\mu(\text{Mo-}K_\alpha) = 0.09$ mm⁻¹.

Crystallographic Measurements.—Crystals suitable for the structural investigation were crystallized from ethyl acetate-ether.⁴ A crystal of dimensions $0.17 \times 0.30 \times 0.50$ mm³ was mounted on a Nicolet R3 four-circle diffractometer (graphite-monochromatized Mo- K_α radiation) and the cell parameters were refined from 21 reflexions, $22^\circ < 2\theta \leq 35^\circ$. The intensities of 1 330 unique reflexions were measured, within $2\theta = 48^\circ$, at room temperature, with the ω -scan technique: scanning speed varying from 1° min^{-1} for the weakest to $10^\circ \text{ min}^{-1}$ for the strongest reflexions; scan ranges 0.5° before and after the peak; the background was measured for 0.8 times the scan time. The intensities of two standard reflexions, monitored every fiftieth measurement, showed no evidence of crystal deterioration; 1 120 reflexions, with $I \geq$

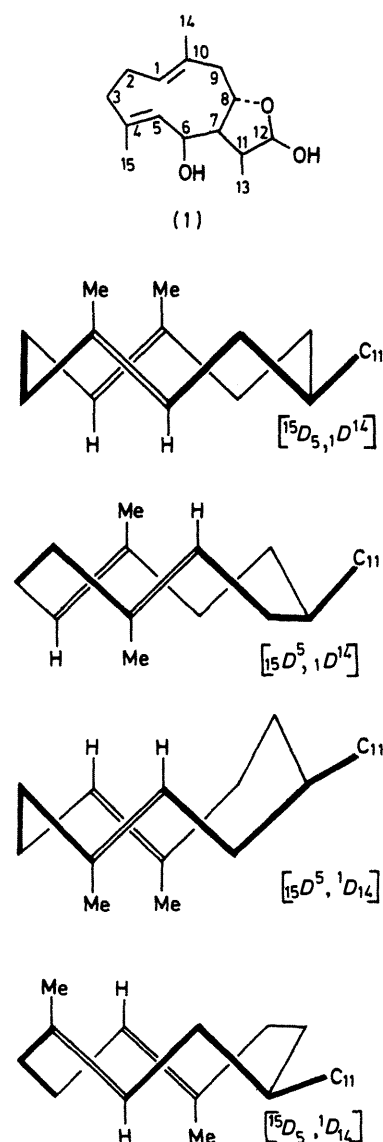


Figure 1. Bidimensional representation of the *trans-trans* diastereoisomers of germacrolides

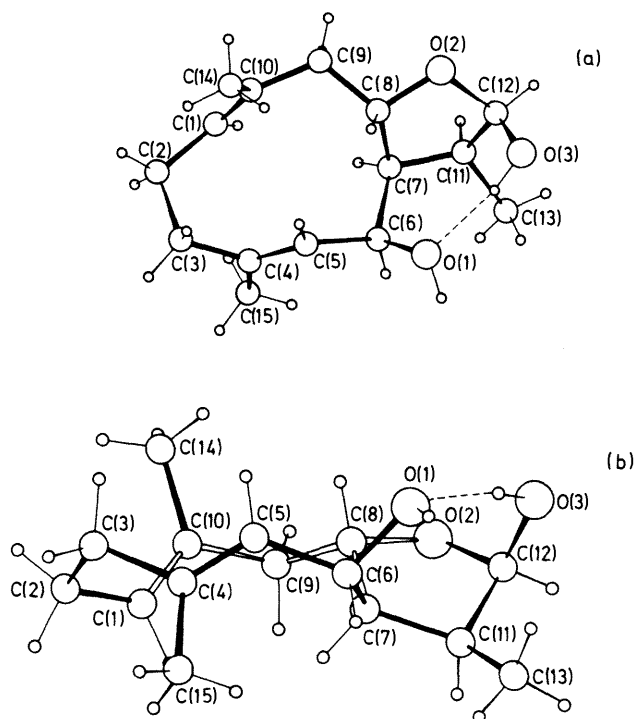


Figure 2. (a) Projection of the molecule of hallerol on the mean plane through the ten-membered ring; (b) view of the molecule of hallerol along a direction perpendicular to the mean plane through the ten-membered ring

$2\sigma(I)$, were used for the analysis; two low-angle reflexions had to be discarded because probably affected by the secondary extinction effect. The intensities were corrected for background and for Lorentz and polarization effects and placed on the absolute scale by statistical methods, using the Syntex (1976)⁵ suite of programs; an empirical absorption correction based on the ψ -scan method⁵ was applied using five reflexions distributed over the range $7^\circ < 2\theta \leq 35^\circ$; the transmission factor varied between 1.003 and 1.012. For all subsequent computations the SHELXTL system⁷ was employed.

Structure Analysis.—The solution was attained by the program RANT:⁸ with 177 $|E|$ values ≥ 1.45 and 2 004 triple-phase relations, the best solution yielded an E -map showing all 18 non-hydrogen atoms. The refinement was by standard least-squares routine. All H atoms were located on a difference Fourier map in the course of the refinement; whilst the H atoms of the three methyl groups were forced to ride on the bonded C atoms, the co-ordinates of the other hydrogens were refined under the constraints C—H = 1.00 ± 0.03 and O—H = 0.98 ± 0.03 Å; adequate constraints were also imposed on the H...H distances and on the distances between the hydrogen and the neighbouring carbon atoms; the thermal parameters were set equal to 1.2 times the equivalent U of the bonded carbon atoms. The weighting scheme for the final cycles was $1/[\sigma(F_o) + GF_o^2]$ where σ is the standard deviation of the F_o and G is a variable to be adjusted after each cycle in order to render the $\Sigma w(\Delta F)^2$ as constant as possible over groups of reflexions batched in several ways. The final value of G was 0.000 42. Convergence (mean shift/e.s.d. = 0.02) was attained at $R = 0.038$, $wR = 0.038$, goodness of fit = 1.374, for 1 118 reflexions and 217 least-squares parameters.

Tables of observed and calculated structure factors,

Table 1. Atom co-ordinates ($\times 10^4$) and temperature factors ($\text{\AA}^2 \times 10^3$)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i>
C(1)	4 307(5)	10 469(3)	4 135(1)	50(1) *
C(2)	4 179(6)	9 803(3)	4 772(2)	62(1) *
C(3)	6 145(6)	8 944(3)	4 835(1)	60(1) *
C(4)	6 709(5)	8 439(2)	4 161(1)	46(1) *
C(5)	8 314(5)	8 914(2)	3 797(1)	42(1) *
C(6)	8 654(5)	8 813(2)	3 058(1)	39(1) *
C(7)	7 380(4)	9 764(2)	2 700(1)	36(1) *
C(8)	7 996(5)	10 974(2)	2 935(1)	41(1) *
C(9)	6 100(6)	11 638(2)	3 267(1)	51(1) *
C(10)	5 761(5)	11 275(2)	3 980(1)	52(1) *
C(11)	7 690(5)	9 839(2)	1 928(1)	44(1) *
C(12)	9 357(6)	10 799(2)	1 850(1)	48(1) *
C(13)	8 300(7)	8 758(3)	1 550(1)	61(1) *
C(14)	7 320(7)	11 797(4)	4 476(2)	84(2) *
C(15)	5 148(6)	7 537(3)	3 916(2)	63(1) *
O(1)	11 009(3)	8 884(2)	2 901(1)	47(1) *
O(2)	8 636(4)	11 591(1)	2 341(1)	55(1) *
O(3)	11 586(4)	10 494(2)	1 935(1)	59(1) *

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

Table 2. Bond lengths (Å) and angles ($^\circ$); e.s.d.s in parentheses

C(1)—C(2)	1.506(4)	C(7)—C(11)	1.564(4)
C(3)—C(4)	1.520(4)	C(9)—C(10)	1.508(4)
C(5)—C(6)	1.504(4)	C(11)—C(13)	1.534(4)
C(7)—C(8)	1.553(4)	C(2)—C(3)	1.565(5)
C(8)—O(2)	1.451(3)	C(4)—C(15)	1.505(4)
C(11)—C(12)	1.523(4)	C(6)—O(1)	1.452(3)
C(12)—O(3)	1.398(4)	C(8)—C(9)	1.537(4)
C(1)—C(10)	1.331(4)	C(10)—C(14)	1.501(5)
C(4)—C(5)	1.334(4)	C(12)—O(2)	1.429(3)
C(6)—C(7)	1.540(4)	O(3)—H(3)	0.94(3)
C(2)—C(1)—C(10)	127.5(3)	C(1)—C(2)—C(3)	111.8(3)
C(2)—C(3)—C(4)	110.7(2)	C(3)—C(4)—C(5)	118.9(3)
C(3)—C(4)—C(15)	115.6(3)	C(5)—C(4)—C(15)	124.9(3)
C(4)—C(5)—C(6)	127.2(3)	C(5)—C(6)—C(7)	109.5(2)
C(5)—C(6)—O(1)	110.0(2)	C(7)—C(6)—O(1)	109.9(2)
C(6)—C(7)—C(8)	114.5(2)	C(6)—C(7)—C(11)	116.4(2)
C(8)—C(7)—C(11)	102.7(2)	C(7)—C(8)—C(9)	115.3(2)
C(7)—C(8)—O(2)	106.2(2)	C(9)—C(8)—O(2)	107.2(2)
C(8)—C(9)—C(10)	111.5(2)	C(1)—C(10)—C(9)	121.0(3)
C(1)—C(10)—C(14)	123.3(3)	C(9)—C(10)—C(14)	115.3(3)
C(7)—C(11)—C(12)	102.9(2)	C(7)—C(11)—C(13)	118.2(2)
C(12)—C(11)—C(13)	114.5(3)	C(11)—C(12)—O(2)	102.6(2)
C(11)—C(12)—O(3)	115.2(2)	O(2)—C(12)—O(3)	112.1(2)
C(8)—O(2)—C(12)	108.5(2)		

anisotropic thermal parameters of the non-hydrogen atoms and hydrogen atoms parameters have been deposited as Supplementary Publication No. 23645 (10 pp.).*

Results and Discussion

Table 1 lists the atomic parameters and Table 2 the bond distances and angles of the non-hydrogen atoms. Figure 2a shows the projection of the molecule on the mean plane through the ten-membered ring and Figure 2b gives the perpendicular view, with the conventional numbering scheme.⁹ The conformation of the ten-membered ring is of the boat-

* For details of the Supplementary publications scheme, see Instructions for Authors (1983), *J. Chem. Soc., Perkin Trans. I*, 1983, Issue 1.

Table 3. Relevant intra- and inter-molecular distances (Å); e.s.d.'s in parentheses

C(1)···C(4)	2.806(4)	C(5)···C(10)	3.211(5)
C(1)···C(5)	3.107(5)	C(4)···C(10)	3.427(5)
O(1)···O(3)	2.743(3)	O(1)···H(3)	1.83(2)
O(1)···O(2) ^a at (\bar{x} , $y - 0.5$, $2.5 - z$)	2.768(3)		
H(1)···O(2) ^a at (\bar{x} , $y - 0.5$, $2.5 - z$)	1.89(2)		

boat type with the C(1)=C(10) and C(4)=C(5) bonds in the parallel orientation; the position of the C(14) and C(15) methyl groups is *anti*- β and α respectively, [$_{15}D^5$, $_{1}D^{14}$].¹ As already mentioned, no other X-ray structural analysis has yet been reported on compounds of this conformation.

The lactol ring is *trans*-fused at C(7)-C(8) and assumes the envelope conformation with C(12) 0.599(2) Å above the mean plane through C(8), C(7), C(11), O(2) (root-mean square deviation = 0.009 Å). The lactol OH group is β -oriented and engaged in a fairly strong intramolecular hydrogen bond with O(1) as acceptor (Figure 2 and Table 3). This bond favours the upward folding of the envelope. The fact that the donor atom is O(3) is consistent with the more acidic nature of the hydroxy group of the lactol moiety.¹⁰ The oxygen atom O(1) is also engaged in an intermolecular hydrogen bond with O(2) of a neighbouring molecule (Table 3).

A few examples of germacrolides showing the parallel boat-boat conformation can be found in the literature.⁹ Among them pertilide² is the only one which has been proved, by an X-ray analysis, to display the above conformation in the solid state. Pertilide is a germacrane sesquiterpene dilactone in which the boat-boat conformation is stabilized by the transannular lactonization involving atoms C(3) and C(14). In hallerol, instead, the boat-boat conformation is stabilized by the formation of the intramolecular hydrogen bond O(3)-H(3)···O(1) which forces the β -oriented O(3) to assume an equatorial position. This position of O(3) brings it closer to O(1) than the axial position and is attainable only when C(15) is on the α face.

The two double bonds in hallerol are in rather close contact (Table 3); the centre to centre distance is here 2.975(3) Å and 2.943(9) Å in pertilide.² The mean deviation from the plane through C(1), C(10), C(4), C(5) is 0.102 Å and the torsion angles C(2)C(1)C(10)C(9) and C(3)C(4)C(5)C(6) are 162.7(3)° and -158.3(3)° (Table 4). All these values compare well with those found in pertilide (the signs of the torsion angles are opposite in the two compounds given the different disposition of the parallel double bonds) and also in our case a certain degree of π - π interaction is possible. This is consistent with the presence of an anomalous absorption band in the u.v. spectrum of hallerol [210 nm (ϵ 1 680)].¹¹

The mean endocyclic distances for the different bond types are: $\langle C(sp^2)=C(sp^2) \rangle = 1.333(4)$; $\langle C(sp^2)-C(sp^3) \rangle = 1.510(4)$; $\langle C(sp^3)-C(sp^3) \rangle = 1.549(4)$ Å. Among the four C(sp²)-C(sp³) distances, both in hallerol and pertilide,² C(3)-C(4) is much longer than the rest: 1.520(3) and 1.528(9) Å against ca. 1.505 Å. The strain in the C(3)-C(4) distance can be justified by decreased overlap of the *p* orbitals owing to the larger deviation from planarity of the C(3)-C(4)=C(5)-C(6) group (torsion angles -158.8(3)°, Table 4, and 155°²). In hallerol two C(sp³)-C(sp³) bonds are longer than expected: C(7)-C(8) = 1.553(4) Å and C(2)-C(3) = 1.565(5) Å; the former bond is even longer in pertilide [1.563(4) Å] and that

Table 4. Relevant torsion angles (°); e.s.d.'s in parentheses

C(10)-C(1)-C(2)-C(3)	-71.3(3)
C(1)-C(2)-C(3)-C(4)	-37.0(2)
C(2)-C(3)-C(4)-C(5)	94.0(3)
C(3)-C(4)-C(5)-C(6)	-158.8(3)
C(4)-C(5)-C(6)-C(7)	90.2(3)
C(5)-C(6)-C(7)-C(8)	56.0(2)
C(6)-C(7)-C(8)-C(9)	-116.2(3)
C(7)-C(8)-C(9)-C(10)	78.7(3)
C(8)-C(9)-C(10)-C(1)	-92.4(3)
C(2)-C(1)-C(10)-C(9)	162.7(3)
C(6)-C(7)-C(11)-C(12)	-101.1(3)
C(7)-C(11)-C(12)-O(2)	-39.7(2)
C(11)-C(12)-O(2)-C(8)	40.4(2)
C(12)-O(2)-C(8)-C(7)	-24.1(2)
O(2)-C(8)-C(7)-C(11)	-1.9(2)

can be justified by the fusion of the two rings; C(2)-C(3) is unexceptional [1.542(4) Å] in pertilide where the strain due to the presence of the double bonds in the cyclodecadiene ring is shared with the lactone ring.

The formation of hallerol by saponification of hallerin⁴ complies with the rule experimentally found to hold for the lactone derivatives: C(6)-C(7) fused lactones with an α -OR function at C(8), when treated with bases, yield C(7)-C(8) fused lactones.¹² Guy *et al.*¹² related this effect to the fact that the lactone ring fused at C(7)-C(8) is more planar and stable. With the present compound the effect obtains even though the lactol moiety does not need to be planar.

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