The Structure and Chemistry of Hallerin, a Mixture of Anomeric Sesquiterpenoids from *Laserpitium halleri* Crantz subsp. *halleri*

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Hallerin (1), the major constituent of the roots of *Laserpitium halleri* Crantz subsp. *halleri*, has been shown to be a mixture of two anomeric sesquiterpene lactols having the (6*S*,7*R*,8*S*,11*S*)-*trans*,*trans*-8-angeloyloxy-6,12-epoxygermacra-1(10),4-dien-12-ol structure. Hallerin (1) and its corresponding lactone (2) in solution adopt a conformation pseudoenantiomeric with that of germacrolides of the costunolide type; this gives rise to elemane and eudesmane derivatives of atypical steric series upon Cope rearrangement and acid-catalysed transannular cyclisation. Saponification of (1) affords (6*S*,7*S*,8*S*,11*S*,12*R*)-*trans*,*trans*-8,12-epoxygermacra-1(10),4-diene-6,12 diol (17) as the sole product. The mechanism and the stereoselectivity of this reaction are discussed in terms of the formation of an intermediate hemiacylal and of the presence of a preferred reacting conformation for the hydroxyaldehyde (22) resulting from its deacylation.

Various oxygenated sesquiterpenes, including a carotane derivative [1] and guaianolides of an atypical steric series,[2] have been isolated, mainly by the Prague group, from plants belonging to the genus *Laserpitium* (Family *Umbelliferae*).

In the course of our studies on alpine plants,[3] we have now examined *L. halleri* Crantz subsp. *halleri*. A chemical investigation of this rare mountain plant led to the isolation of a viscous, chromatographically homogenous oil, which was called hallerin and shown to be a mixture of two anomeric sesquiterpene intramolecular hemiacetals. We present here the structural elucidation and chemical properties of these compounds, which are the first sesquiterpenes bearing a C-7 isopropyl side-chain oxidized to a lactol function isolated so far from plants.†

Upon treatment with acids, hallerin (1) developed a deep green colour, similar to that of some furan derivatives;[4] its i.r. spectrum revealed the presence of hydroxy group(s) (broad bands at 3 600 and 3 400 cm^{-1}) and a α,β-unsaturated ester (1 710 cm^{-1}). High-resolution mass spectroscopy (h.r.m.s.) showed a molecular weight of 334.2123, corresponding to the molecular formula $C_{20}H_{30}O_4$; the presence of fragmentation peaks at 251 $(M - 83)^+$, 234 $(M - 100)^+$, 83, and 55 suggested the presence of a hemiterpene ester group. The latter was confirmed as an angelate group ‡ by the presence in the ^1H n.m.r. spectrum of a split vinyl proton at δ 6.08 (qq).[5] The u.v. spectrum exhibited only end absorption characteristic of α,β-unsaturated esters [$\lambda_{max.}$ (EtOH) 215 (log ε 3.8)].

The ^1H n.m.r. spectrum was surprisingly complex, showing two sets of signals which corresponded to two compounds in a *ca.* 7 : 6 ratio; also the ^{13}C n.m.r. spectrum displayed an unexpected number of signals, owing to the doubling of each peak. The most remarkable characteristic of the ^{13}C n.m.r. spectrum was the presence of 2 doublets at *ca.* 100 p.p.m. (δ 99.56 and 104.7 respectively). These signals constituted the best separated couple, and their chemical shift and multiplicity were comparable with those of the anomeric carbons of sugars.[6] The presence of a hemiacetal function was further supported by a positive Tollens test, while the oxidation of (1) to a γ-lactone (2) (ν_{CO} 1 770 cm^{-1}), established that the hemiacetal was of the furan type. Since (2) was a chromatographically and spectroscopically homogeneous product, hallerin was a mixture of two anomeric sesquiterpene lactols. These compounds, although inseparable by chromatography (t.l.c., h.p.l.c.), were not in equilibrium, as shown by variable-temperature ^1H and ^{13}C n.m.r. experiments.§

Spin-decoupling experiments, starting with the doublet at δ 1.26 (13-H), allowed location through irradiation of 11-H [δ 2.70 (m)] of the signal of 7-H [δ 2.10 (m)], and then 6-H (δ 4.92 (dd) and 5-H [δ 4.77br (d)] on one side, and 8-H [δ 5.44 (dq)], 9a-H [δ 2.82br (dd)] and 9b-H [δ 2.00br (dd)] on the other. Irradiation of the allylic protons 9a-, b-H and the olefinic proton 5-H identified the two 3-protons broad singlets at δ 1.36 and 1.15 as the allylic methyls 14-H and 15-H respectively. A broad triplet at δ 4.97 was assigned to the olefinic proton 1-H on account of its sharpening upon irradiation of 14-H.

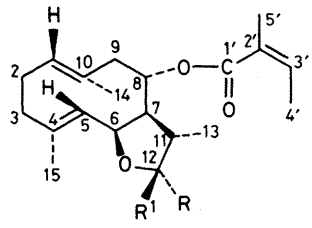
These data could fit either of the two isomeric germacrane-type constitutional formulae A and B. Formula A was chosen as follows. Except for heliangolides, C-6 and C-8 lactone hydrogens generally resonate at higher field than the corresponding ones of an ester chain [7]; n.O.e. experiments showed that both endocyclic double bonds in (2) were *trans*, thus ruling out a heliangolide-type configuration. Therefore 6-H at δ 4.92 was identified with the hydrogen on the carbon carrying the lactone group, and 8-H at δ 5.44 with the hydrogen on the carbon bearing the angelate group. Furthermore, C(8)-germacrolides are conformationally mobile, and their ^1H n.m.r. spectra are generally not well resolved at room temperature on account of slow conformational equilibriation;[8] (2), a C(6)-germacrolide, was instead conformationally stable, and displayed a well-resolved ^1H n.m.r. spectrum, with sharp lines.

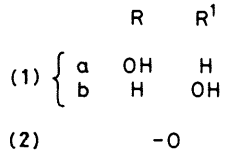
Stereochemistry was deduced in the following way. The isopropyl side-chain at C-7 was assigned a β configuration on

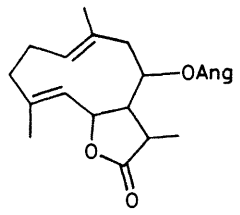
† A nardosinane derivative with a lactolized C-7 side-chain has been isolated from the soft coral *Lemnalia africana* (B. W. Bowden, J. C. Coll, S. J. Mitchell, B. W. Skelton, and A. H. White, *Aust. J. Chem.*, 1980, **33**, 2737); an eremophilane containing an analogous group in the form of a methyl acetal has been isolated from *Petasites hybridus* Fl. Wett.[4]

‡ Angelate = (*Z*)-2-methylbut-2-enoate.

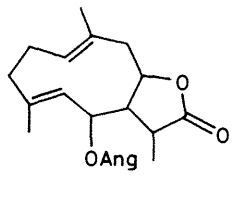
§ A positive Tollens test could be ascribed to the use of an excess of base and heating: under these conditions the hemiacetal ring is opened, and the transposed lactol (17) was shown to be present in the reaction mixture. Attempted use of Tollens reaction for preparative purposes was unsuccessful, owing to the formation of mixtures of products.







A



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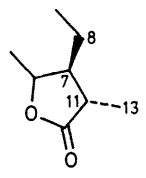
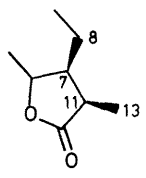


C



D

biogenetic grounds;[9] the angelate group was then assigned an equatorial position (α on the basis of the preceding assumption) because of the eight-peak pattern of its geminal hydrogen, which constituted the X part of a ABMX spin system, resulting from its interaction with 2 axial ($J_{7,8}$ 11 Hz, $J_{8,9b}$ 9 Hz) and one equatorial ($J_{8,9b}$ 5 Hz) protons. $J_{5,6}$ Was large (10 Hz), indicating a diaxial interaction between these two hydrogens; $J_{6,7}$ was smaller (7 Hz), suggesting instead a *cis* relationship between 6-H and 7-H. The *cis* nature of the lactone junction was further supported by the c.d. of (2): *cis* C(6)-germacrolides assume a boat-chair conformation ($_{15}D^{5},^{1}D_{14}$)[8] which is pseudoenantiomeric with the double-chair conformation ($^{15}D_{5,1}D^{14}$) of *trans*-$C_{(6)}$ germacrolides[10,11] (Scheme 2); this gives rise to a Cotton effect, associated with homoconjugative overlapping of the endocyclic double bonds, of sign opposite to that of *trans* C(6)-germacrolides.[10,11] In keeping with this, (2) exhibited a *negative* Cotton effect at 210 nm ([θ] = −65 300°), while *trans* C(6)-germacrolides show a *positive* Cotton effect at a similar position.[10,11]

Although $J_{7,11}$ was known (5 Hz), the relative configuration at C-11 could not be determined solely on the basis of the ^{1}H n.m.r. spectrum: application of the Karplus equation gave ambiguous results and, furthermore, *cis* γ-lactone rings give rise to considerable angle distortion.[12] The α-methyl configuration at C-11 was established on the basis of ^{13}C n.m.r. data. It had already been noted that in compounds of the eudesmane series the chemical shift of an α 11-CH_3 is generally >10 p.p.m. (usually 12—15 p.p.m.), while that of a β 11-CH_3 is generally <10 p.p.m.[13] Inspection of literature data[14] also showed that in other sesquiterpene lactone type skeletons a C-11 α-methyl group is deshielded compared with a β-methyl group. A more general relationship seems therefore to hold, allowing assignment of an α configuration to C-11 methyl group resonances >12.5—13 p.p.m., and a β conformation to C-11 methyl group resonances <10 p.p.m.* In the case of C-6 closure, the succession C(8)–C(7)–C(11)–C(13) constitutes, in fact, a butane-like fragment, frozen in a relatively fixed conformation by the lactone junction.† In lactones with an α 11-methyl group, this fragment is of the *trans*-type (C), while in β 11-methyl lactones it is of the gauche-type (D). It is well established that the terminal atoms (in this case C-8 and C-11) of a gauche butane-like fragment are shielded compared with those of a *trans* butane-like fragment.‡[15] As can be judged from Table 2, all the compounds of the hallerin series [C(6)-closure) have δ(C-13) in the 14—17 p.p.m. range, and therefore must all have an α 11-CH_3. This configuration at C-11 was further supported by application of the solvent-shift rule[12] to the rigid *trans*-decalin derivative (4), obtained along with its $\Delta^{4,15}$ isomer (5) upon epoxidation of (2) and cyclization of the resulting epoxide (3); the upfield shift of the 13-H doublet while changing from $CDCl_3$ to C_6D_6 was 0.16 p.p.m., thus requiring a pseudoequatorial (α) methyl group.[12]

The product of oxidation of hallerin was therefore represented by the stereostructure (2); thus hallerin was a mixture of the anomeric compounds (1a) and (1b) §. On the basis of the c.d. curve, it is probable that these formulae also represent the absolute configuration of these products.

The pyrolysis of *trans*, *trans*-germacra-1,5-dienes proceeds in a highly stereospecific way, generally giving mixtures of the starting material and the Cope rearrangement product.[17] However, in the case of (1) and (2), the corresponding elemane derivatives (10) and (11) were obtained in quantitative way, with no trace of the starting compounds in the reaction mixture. This behaviour has already been noted for the C(6)-germacrolide ursiniolide B,[10] which has the same conformation as (1) and (2). Upon application of the generalized lactone rule,[18] Samek *et al.* concluded that Cope rearrangement of ursiniolide B was accompanied by the conformational inversion of the fragment C(5)···C(10), whose flipping from the boat to the chair conformation drives the equilibrium of the Cope transposition towards the formation of the rearranged product.[10]

Comparison of the ^{1}H n.m.r. spectra of (2) and (11) fully confirms this interpretation; in the course of the trans-position, 7-H, 8-H, and 9-H had moved, in fact, from axial to equatorial positions, as clearly shown by the changes in the pattern of 8-H going from (2) to (11). In (2) 8-H was a well-resolved doublet of quartets, with $J_{7,8}$ 11 Hz, $J_{8,9a}$ 9 Hz, and $J_{8,9b}$ 5 Hz; in (11) this proton was instead a much narrower signal, with $J_{7,8} = J_{8,9a} = J_{8,9b}$ <3 Hz. The equatorial position of 7-H was further supported by the high value of $J_{7,11}$ in (11) (13 Hz), which requires an antiperiplanar relationship between these 2 protons, which is only possible if 7-H is equatorial relative to the carbocyclic ring. The electronic and conformational changes involved in the pyrolysis of (2) are depicted in Scheme 1.

Guaianolides with a *cis* carbocyclic junction (1Hβ,5Hβ)

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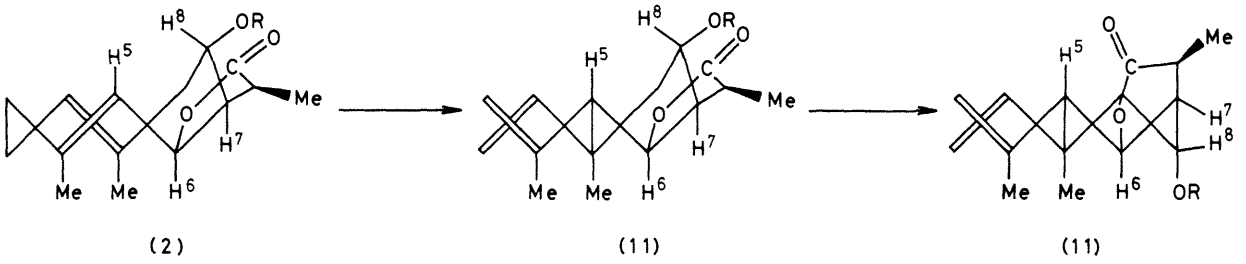
* Intermediate cases, in which 11-CH_3 resonates between 10 and 12 p.p.m. are known (W. Herz, J. S. Prasad, and J. F. Blount, *J. Org. Chem.*, 1982, **47**, 3991). In these cases, of course, this relationship is not applicable.

† In the case of C-8 closure, the succession C(6)–C(7)–C(11)–C(13) must be inspected.

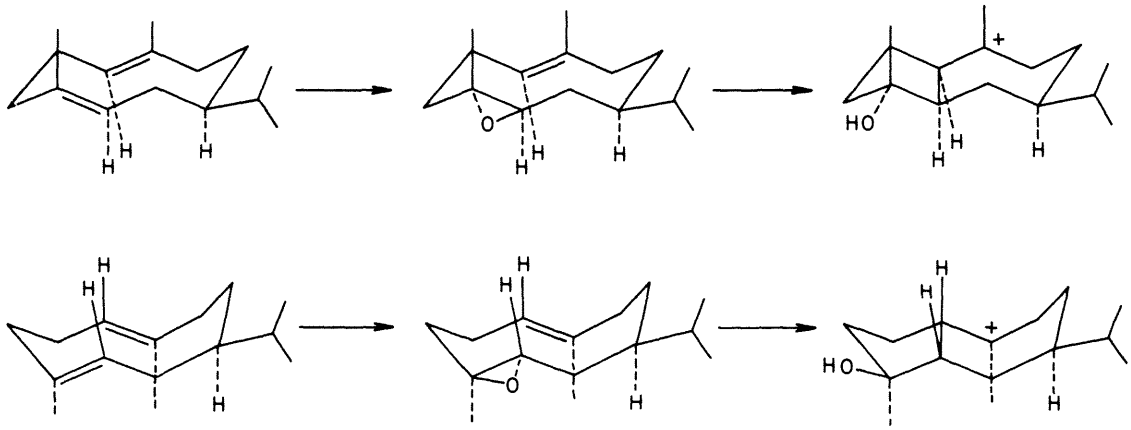
‡ A similar argument has been used to establish the stereochemistry of 1,2-dimethylcyclopentanes by ^{13}C n.m.r. spectroscopy (H. J. Schneider, N. Nguyen-Ba, and F. Thomas, *Tetrahedron*, 1982, **38**, 2327).

§ The bidimensional representation of hallerin and its derivatives was based on established rules (D. Rogers, G. P. Moss, and S. Neidle, *J. Chem. Soc., Chem. Commun.*, 1972, 142; ref. 16, pages 59—61 and, in part, P. J. De Clercq, *Tetrahedron*, 1981, **37**, 4277). Symbolic ' crown ' representations in Schemes 1 and 5 were drawn according to ref. 8.



(2) (11) (11)

Scheme 1.



Scheme 2. Possible biogenesis of 1αH,5αH- and 1βH,5βH-guaianes

pseudoenantiomeric with the one of the common guaianolides (1Hα,5Hα), have been found in plants of the genus *Laserpitium*[2]; these two structural types of guaianolides might derive from germacrane precursors adopting pseudoenantiomeric conformations: 1Hα,5Hα-guaianolides are believed to result from the transannular cyclization of the 4,5-epoxides of germacrolides in the ($^{15}D_{5,1}D^{14}$) conformation;[16] the same reaction scheme applied to the 4,5-epoxides of germacrolides in the ($_{15}D^{5},^{1}D_{14}$) conformation would lead to 1Hβ,5Hβ-guaianolides (Scheme 2).

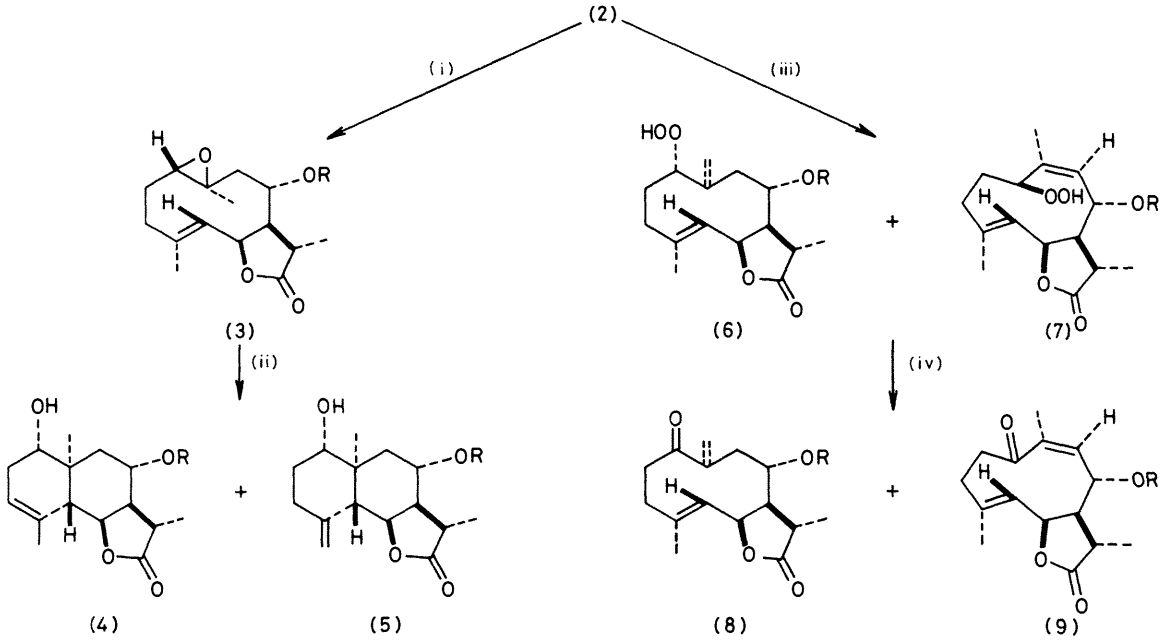
In order to test this biogenetic hypothesis, we tried to obtain derivatives of (2) bearing oxygenated functions at C-4, and thus susceptible to transannular cyclization of this type. Both epoxidation and photo-oxygenation of (2) were unsatisfactory in this regard, since only the C(1)–C(10) double bond was affected in these reactions. Epoxidation of (2) with 1 equiv. of *meta*-chloroperbenzoic acid (MCPBA) afforded a mixture of the epoxide (3) and the eudesmanolides (4) and (5), resulting from the further transannular cyclization of (3). The latter was obtained as sole product when the reaction was carried out in the presence of powdered sodium acetate; it was then transformed into (4) and (5) by treatment with mineral (dilute HCl) or Lewis ($BF_3{\cdot}Et_2O$) acids. Compounds (4) and (5) belong to the class of the so called *ent*-eudesmanes.[19] It is worth noting that only one C(6) *ent*-eudesmanolide was formerly known[20], and this isolated from a plant belonging to the genus *Laserpitium*.[20] The formation of (4) and (5) is readily understood from the ($_{15}D^{5}$,-$^{1}D_{14}$) conformation of (2) (Scheme 3).

Photo-oxygenation of (2) afforded a 3 : 1 mixture of the *exo*/*endo* isomeric hydroperoxides (6) and (7), which were separated after conversion into the corresponding α,β-unsaturated ketones (8) and (9). The high value of $J_{8,9}$ (11 Hz) in (9) showed that these protons were *trans*-diaxial and, therefore, that 9-H was on the α plane of the molecule. Since an ' ene ' reaction most probably proceeds with a *cis* concerted mechanism, maintaining the original orientation of the substituents of the olefin,[21] the double bond C(9)–C(10) was *cis* (*Z*), as the 10-methyl was on the α plane of the molecule in (2).

The esters (2) and (11) were hydrolysed very slowly, so that after 7 days at room temperature in a 5% methanolic solution, 28% of (2) and 32% of (11) were recovered unchanged. Saponification of (2) afforded, besides the starting compound, a complex mixture from which no pure compound was isolable; in the case of (11), besides starting material, the hydroxyelemanolide (12) was obtained in 40% yield. Under these hydrolysis conditions, 7,6-lactonized germacrolides bearing an 8α oxygen function always relactonize to C-8.[22] This general relactonization rule does not seem to hold for elemanolides, since the C-6 lactonization was maintained in the course of the saponification of (11). The signal of the 11-methyl in (12) was, in fact, at 14.42 p.p.m., thus still indicating an α orientation of the 11-methyl group.*

The C-6 lactone junction was further supported by comparison of the ^{1}H n.m.r. spectra of (12) and its ester (13), formed upon *in situ* addition of trichloroacetyl isocyanate (TAI) to a $CDCl_3$ solution of (12).[23] Formation of the ester had moved downfield (1.2 p.p.m.) the enlarged 8-H signal, while the 6-H doublet of doublets was practically unaffected. In keeping with a C-6 closure, oxidation of (12) afforded the ketolactone (14), which gave a positive Zimmermann test.[24] Compound (14) was very unstable, and underwent quantitative conversion into the ketoacid (15) on being kept in contact with silica gel.

* Relactonization at C-8 involves a 180° rotation of the C-7 side-chain along the C(7)–C(11) bond, and therefore inversion of the orientation of the methyl group at C-11. In the formation of a C-8 lactone from a C-6 lactone bearing an α 11-CH_3, the resonance of this group should so move upfield, to below 10 p.p.m.



Scheme 3. i, MCPBA, NaOAc; (ii), HCl (BF_3·Et_2O); iii, *hv*, O_2, sens.; iv,Ac_2O, pyr. R = angelate

While saponification of (2) and (11) in methanolic KOH was very slow, under similar conditions the corresponding lactols (1) and (10), underwent a more rapid hydrolysis particularly the former which was totally saponified in 14 h.

Saponification of (10) afforded the expected mixture of anomers (16), whose structures were established by oxidation to the ketolactone (14). In the case of (1), a crystalline material was obtained. Surprisingly this product (17), which we called hallerol, was homogeneous, as shown by its ^{13}C n.m.r. spectrum, which displayed only a single set of signals. In the course of the reaction the lactol junction had moved from C-6 to C-8, as shown by the upfield shift of the 11-methyl group, which was now at δ 9.38; according to the chemical shift of C-12 (δ 99.39), (17) was the β-anomer.[6]

At room temperature the ^1H n.m.r. spectrum of (17) displayed broad and not well-resolved signals. Exchange with D_2O caused two signals to disappear (δ 5.50 and 4.00). The one at lower field was the hydrogen of the hemiacetalic hydroxy group since it was absent in the spectrum of the methyl derivative (18). The low position of these signals suggested the presence of a strong intramolecular hydrogen bond between the alcoholic and the hemiacetalic hydroxy groups. The broadening of signals in the ^1H n.m.r. spectrum of (17) showed that this compound existed in solution at room temperature as a mixture of interconverting rotamers.[8]

In order to freeze these conformational equilibria, (17) was subjected to epoxidation.* Treatment with 1 and 2 equiv. of MCPBA gave the monoepoxide derivative (19) and the diepoxide derivative (20) respectively.† On the basis of their ^1H n.m.r. spectra which displayed well-resolved signals, both (19) and (20) appeared to exist in solution at room temperature as single conformers. Double-resonance experiments allowed assignment of almost all the signals in the spectrum of (19). The C-8 closure could thus be unambiguously confirmed by transformation of (19) into its derivative (21), and comparing the spectrum of the diester with that of the starting compound.

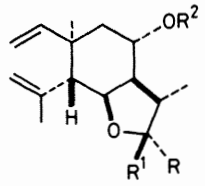
Since the saponification of (1) and (10) was fast compared with that of the corresponding lactones (2) and (11), it was clear that the hemiacetal group was involved in the reaction. The formation of a C(8)-lactol from a C(6)-lactol showed that under these conditions of saponification the lactol ring was open to give an aldehyde, in equilibrium with its hydrated form. The attack of the latter on the angelate, affording a more easily saponifiable hemiacylal, could follow, while reclosure of the lactol ring would complete the reaction (Scheme 4).

In the case of compound (1) however, the possibility of an intramolecular B_{AL2} mechanism, involving attack of the hydrated form of the aldehyde on C-8 could not be disregarded, the lactol junction being at this carbon in the saponification product (17). Since the stereochemistry at C-8, which in the case of a B_{AL2} mechanism would have been inverted, was not unambiguously derivable from the ^1H n.m.r. data alone,‡ an *X*-ray diffraction study of (17) was undertaken; the results showed that this compound exists in the solid state as a boat-boat conformer of the ($_{15}D^5$,$_1D^{14}$) type having a C-8 *trans*-lactol junction.[25] It seems therefore that both (1) and (10) are saponified by the same mechanism: the formation of (17) as the sole anomer in the course of the saponification of (1) can be rationalized assuming that the

* Epoxidation of a double bond of a germacrolide locks the conformation of the segment of the molecule in which the double bond lies, since conformational inversion would cause now the epoxide oxygen to be inside the ring, and therefore subjected to prohibitive transannular crowding.

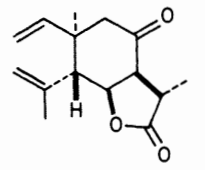
† Since only one monoepoxide was obtained upon treatment with 1 equiv. of MCPBA, one rotamer of (17) reacts with this reagent preferentially. This behaviour has already been observed for the conformationally mobile germacrolide isabelin (W. Herz, P. S. Subramaniam, P. S. Santhanam, K. Aota, and A. L. Hall, *J. Org. Chem.*, 1970, **35**, 1453.)

‡ The coupling constants of 8-H with its vicinal protons were for compound (19), 4 Hz ($J_{7,8}$), 4 Hz ($J_{8,9b}$), and 11 Hz ($J_{8,9a}$). Owing to the possibility of several different conformations, both *cis*- and *trans*-C(8)-germacranolides can display these values of coupling constants, as shown by the case of simsiolide (F. Bohlmann and C. Zdero, *Phytochemistry*, 1977, **16**, 766) and its C-8 epimer (F. Shafizadeh and N. R. Bhadane, *Phytochemistry*, 1973, **12**, 857).

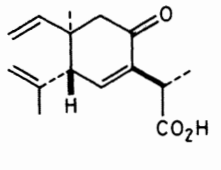


		R	R^1	R^2
(10)	a	OH	H	Ang
	b	H	OH	Ang
(11)		-O		Ang
(12)		-O		H
(13)		-O		TAC
(16)	a	OH	H	H
	b	H	OH	H

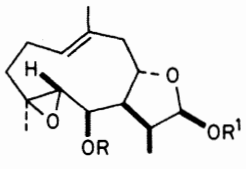
TAC = $CCl_3CONHCO-$



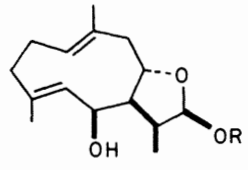
(14)



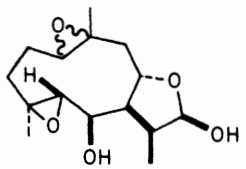
(15)



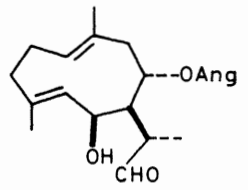
	R	R^1
(19)	H	H
(21)	TAC	TAC



	R
(17)	H
(18)	CH_3



(20)



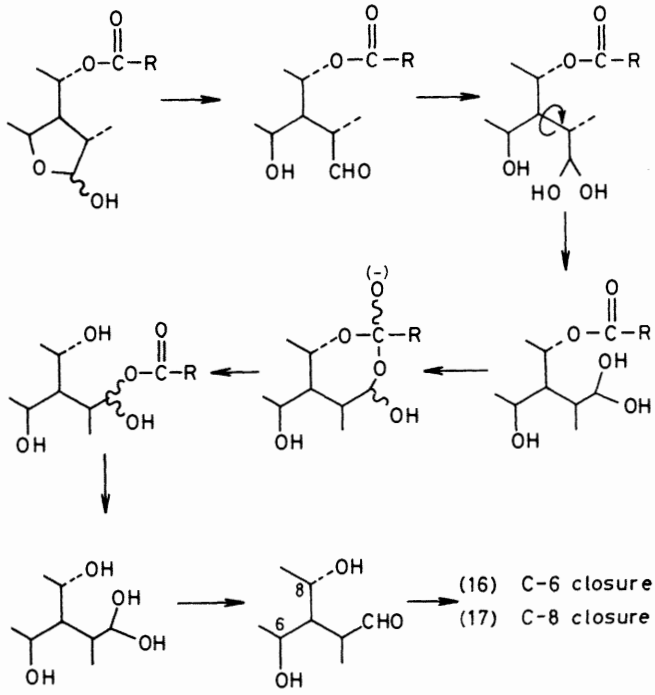
(23)

intermediate aldehyde (22) adopts in solution a conformation with the carbonyl group hydrogen-bonded to the 6-hydroxy group. This bonding, which is maintained in (17) both in solution and in the solid state,[25] is only possible if the carbonyl group is oriented towards the ten-membered ring, on the β side of the five-membered incipiently forming lactol ring (Scheme 5).*

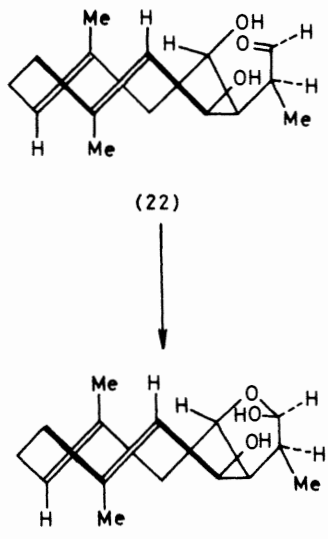
It is not clear whether the anomeric constituents of hallerin are natural products or artefacts formed in the course of the extraction from the hydroxyaldehyde (23), a stabilized form of which (*e.g.* a labile O-6 ester or glucoside) might exist in the plant. However, extraction of fresh plant material with non acidic solvents such as light petroleum or diethyl ether, or polar solvents (methanol, ethanol, ethyl acetate) failed to reveal the presence of a compound of this type, as judged from t.l.c. and ^1H n.m.r. analysis of the extracts so obtained.

Experimental

M.p.s were determined on a Büchi SMP-20 apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 automatic polarimeter in $CHCl_3$ solution, except for compound (20). C.d. spectra were taken on a Jobin Yvon Mark III apparatus in methanolic solution. High- and low-resolution mass spectra were obtained on a Cratos MS 80 and a Varian Mat CH7 A apparatus respectively. U.v. spectra were taken for 95% EtOH solutions on a Beckman DB-GT spectrophotometer. I.r. spectra were recorded on a Perkin-Elmer model 237 spectrophotometer. ^1H N.m.r. spectra (Table 1) were obtained on a Varian XL 200 spectrometer. ^{13}C N.m.r. spectra (Table 2) were taken on a Varian XL 200 or Varian XL 100 spectrometer. Silica gel 60 (70—230 mesh) (Merck) was used for the column chromatography



Scheme 4. Mechanism of the alkaline hydrolysis of the anomeric mixtures (1) and (10)



(22)

(17)

Scheme 5.

* For an example of unexpected stereoselective closure of an acetalic ring in the field of sesquiterpenes, see A. F. Thomas and R. Dubin, *Helv. Chim. Acta*, 1974, **57**, 223.

separations. Analytical and preparative (thickness : 2 mm) t.l.c. was performed on Silica gel G F254 pre-coated plates (Merck). Spots were revealed by spraying with H_2SO_4 and heating at 100 °C. The preparative h.p.l.c. separation of compounds (8), and (9) was performed on a Perkin-Elmer series 3B liquid chromatograph equipped with an LC-75 spectrophotometric detector and a LC-75 autocontrol. A Perkin-Elmer preparative (10 μm) column (25 × 3 cm I.D.) was used.

Plant Material.—*L. halleri* subsp. *halleri* was collected near Valnontey and Lillaz (Cogne, Valle d'Aosta, Italy) during the years 1981—1982. Plant material was identified by P. A. Silvio Stefenelli. A voucher specimen is held at the herbarium of the Giardino Botanico Alpino Paradisia, Valnontey, Cogne, Italy.

Isolation of Hallerin (1).—Dried ground roots (700 g) were extracted with $CHCl_3$ at room temperature (6 × 3l). Removal

Table 1. ^1H N.m.r. results determined at 200 MHz with $SiMe_4$ as internal standard. Chemical shifts given as δ values with *J* in Hz (in parentheses). The symbol x refers to signals that could not be observed because of overlapping. Trichloroacetyl isocyanate (TAI) was added to $CDCl_3$ solutions of (12) and (19) as described in ref. 23

Compound:	(2) *		(3) *	(4) *
Solvent:	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
1-H	5.15br t (8.0)	4.97tq (7.6, 2.0)	2.94 (dd, 8.0, 5.3)	3.18 (dd, 9.0, 6.3)
2a-H	x	x	x	x
2b-H	x	x	x	x
3a-H	x	x	x	5.18br (s)
3b-H	x	x	x	
5-H	4.95br (d, 10)	4.77br (dq, 10, 1.0)	5.50br (d, 10)	1.60br (d, 9.5)
6-H	5.25 (dd, 10, 7.3)	4.92 (dd, 10, 7.0)	5.32 (dd, 10, 7.5)	4.18 (dd, 9.5, 7.0)
7-H	2.46 (m)	2.10 (m)	x	x
8-H	5.33 (dq, 11, 9.0, 4.2)	5.44 (dq, 11, 9.0, 5.0)	5.40 (dq, 11, 8.5, 4.4)	5.00 (q, 4.0, 2.0, 2.0)
9a-H	2.83br (dd, 13, 11)	2.82br (dd, 13, 11)	x	1.26 (dd, 13, 2.0)
9b-H	1.87br (dd, 13, 4.2)	x	x	x
11-H	2.75m (8.0, 5.0)	2.70 (m, 8.0, 5.0)	x	x
12-H				
13-H	1.53 (d, 8.0)	1.26 (d, 8.0)	1.30 (d, 8.0)	1.18 (d, 6.5)
14-H	1.69br (s)	1.36br (s)	1.10 (s)	0.90 (s)
15-H	1.45br (s)	1.15 (d, 1.0)	1.76br (s)	1.90br (s)

Compound:	(8) *	(11) *	(11) *	(12)
Solvent:	$CDCl_3$	$CDCl_3$	C_6D_6	$CDCl_3$
1-H		5.72 (dd, 11, 18)	5.58 (dd, 11, 18)	5.75 (dd, 11, 16)
2a-H	x	4.98 (d, 11)	4.88 (d, 11)	4.98 (d, 11)
2b-H	x	4.93 (d, 18)	4.03 (d, 18)	4.92 (d, 16)
3a-H	x	4.75br (s)	4.72br (s)	4.76br (s)
3b-H	x	5.05br (s)	5.05br (s)	5.05br (t, 1.6)
5-H	5.10br (d, 8.0)	x	1.78 (d, 10)	2.07 (d, 10)
6-H	4.86 (dd, 8.0, 6.3)	4.85 (dd, 10, 7.0)	4.42 (dd, 10, 7.5)	4.87 (dd, 10, 7)
7-H	x	x	2.10 (m, 7.5, 13, 2.3)	2.40 (m)
8-H	5.28 (td, 9.6, 9.6, 3.0)	5.25br (m)	4.99br (m)	4.12br (q, 4.80, 4.80, *ca.* 2)
9a-H	x	x	1.42br (s)	1.80 (dd, 4.8 15)
9b-H	x	x	1.44br (s)	1.60 (dd, 15, 4.8)
11-H	x	x	1.90 (dq, 13, 7.0)	x
12-H				
13-H	1.08 (d, 7.5)	1.38 (d, 7.0)	1.20 (d, 7.0)	1.31 (d, 6.5)
14-H	5.46; 5.56br (s)	1.16 (s)	0.99 (s)	1.17 (s)
15-H	1.54br (s)	1.80br (s)	1.70br (s)	1.77br (s)

Compound:	(14)	(14)	(15)	(17) †
Solvent:	$CDCl_3$	C_6D_6	$CDCl_3$	$CDCl_3$
1-H	5.77 (dd, 17, 11)	5.38 (dd, 11; 17)	5.88 (dd, 17, 11)	5.07br (m)
2a-H	5.06 (d, 11)	4.72 (d, 11)	5.03 (d, 11)	x
2b-H	4.94 (d, 17)	4.58 (d, 17)	4.80 (d, 17)	x
3a-H	5.11br (s)	4.97br (s)	5.09br (s)	x
3b-H	4.82br (s)	4.58br (s)	4.80br (s)	x
5-H	2.34 (d, 11)	1.83 (d, 10)	3.08 (d, 5.0)	4.90br (d, 7.5)
6-H	4.92 (dd, 11, 7)	4.15 (dd, 10, 7.5)	6.54 (d, 5.0)	4.52br (d, 7.5)
7-H	3.00 (12, 7.0)	2.38 (m)		x
8-H				4.20br (d, 10)
9a-H	2.70 (d, 15)	x	2.45 (s)	x
9b-H	2.24 (d, 15)	x		x
11-H	2.80 (m)	x	3.5 (q, 7.5)	x
12-H				5.10 (d, 4.80)
13-H	1.18 (d, 7.5)	1.08 (d, 7.5)	1.30 (d, 7.5)	1.09 (d, 7.5)
14-H	0.92 (s)	0.53 (s)	1.06 (s)	1.65br (s)
15-H	1.70br (s)	1.56br (s)	1.75br (s)	1.50br (s)

Table 1 (*continued*)

Compound:	(18) †	(19) ‡	Δ(TAI)	(20)
Solvent:	$CDCl_3$	$CDCl_3$		$CDCl_3$ + C_5D_5N 5 : 1
1-H	4.95br (t, 7.5)	5.33br (t, 7.5)	+0.07	3.00 (dd, 9.0, 5.0)
2a-H	x	x		x
2b-H	x	x		x
3a-H	x	x		x
3b-H	x	x		x
5-H	4.88 (d, 7.0)	2.47 (d, 8.0)	+0.08	2.83 (d, 9.0)
6-H	4.50br (d, 7.0)	3.53 (dd, 8.0, 1.5)	+1.32	3.65 (dd, 9.0, 2.0)
7-H	x	2.05 (m)		x
8-H	4.10br (d, 10)	4.30 (dt, 11, 4.0, 4.0)	+0.30	4.68 (dq, 11, 5.0, 3.3)
9a-H	x	2.00 (dd, 15, 4.0)		2.10 (dd, 13, 3.3)
9b-H	x	1.95 (dd, 15, 11)		2.52 (dd, 13, 5.0)
11-H	x	x		x
12-H	4.80br (d, 4.5)	5.15 (d, 4.8)	+1.15	5.10 (d, 4.8)
13-H	1.04 (d, 7.5)	1.06 (d, 7.5)	+0.05	1.10 (d, 7.5)
14-H	1.60br (s)	1.65br (s)	+0.02	1.38 (s)
15-H	1.45br (s)	1.23 (s)	+0.10	1.30 (s)
OCH_3	3.38 (s)			

* The proton signals for the angelate group were almost identical for all the compounds containing this group. Those observed in (2) are given as representative: δ($CDCl_3$) 6.10 (qq, 7.0, 1.5, 3′-H), 2.00 (dq, 7.0, 1.5, 1.5, 4′-H), 1.88 (quint., 1.5, 1.5, 5′-H); δ(C_6D_6) 5.76 (qq, 7.0, 1.5, 3′-H), 2.00 (dq, 7.0, 1.5, 1.5, 4′-H), 1.86 (quint. 1.5, 1.5, 5′-H). † Taken at 45 °C after exchange with D_2O. ‡ Taken after exchange with D_2O.

of the solvent left a red, thick syrup (96 g), part of which (48 g) was separated on a silica gel column (400 g). Elution with $CHCl_3$ gave hallerin (13 g, 3.40% on dried plant material).

A pale yellow, pungent oil $[\alpha]_D^{25}$ −68°; $\nu_{max.}$ ($CHCl_3$) 3 600, 3 400 (hydroxy) and 1 710 (α, β-unsaturated ester); $\lambda_{max.}$ 215 (log ε 3.9); *m/z* (relative intensity) 334.2123 ($C_{20}H_{30}O_4$ requires 334.2144) (0.1%), 251 $(M - 83)^+$ (20%), 234 $(M - 100)^+$ (60%); 83 $(C_5H_7O)^+$ (100%), and 55 $(C_4H_7)^+$ (84%).

Oxidation of Hallerin (1).—To a stirred suspension of pyridinium chlorochromate (2.264 g, 10.5 mmol) and powdered sodium acetate (0.13 g, 1.58 mmol) in dry CH_2Cl_2 (10 ml), (1) (1.823 g, 5.45 mmol) dissolved in dry CH_2Cl_2 (2 ml) was added in one step. After 2 h dry CH_2Cl_2 (15 ml) was added, and the supernatant liquid was decanted from the black gum. The organic solution was passed through a short pad of Florisil, washed successively with dilute HCl and water and then dried ($MgSO_4$). Removal of the solvent left a yellowish oil (1.465 g) which was crystallized from light petroleum (b.p. 40—60 °C) to give (2) as a white powder (998 mg). Chromatography of the mother liquors (Si gel, elution with $CHCl_3$) afforded additional (2) (220 mg, total yield: 67%), m.p. 104—106 °C, $[\alpha]_D^{25}$ −166° (*c* 1.05), $\nu_{max.}$ (KBr) (no OH band), 1 770 (γ-lactone), 1 710 (α,β-unsaturated ester), 1 670, 1 650 (double bonds); $\lambda_{max.}$ (log ε 4); *m/z* (rel. int.): 332.1972 ($C_{20}H_{28}O_4$ requires 332.1987) $(M)^+$ (2%) and 83 $(C_5H_7O)^+$ (100%).

Cope Rearrangement of Hallerin (1).—Hallerin (1) (1 g) was heated under a water pump vacuum at 180 °C in a sublimation tube. After 5 min the tube was rapidly cooled with a flow of cold air. A pale yellow oil was obtained, which, on the basis of t.l.c. and ^1H n.m.r. evidence, showed no trace of starting material: filtration through a short pad of silica gel removed some polymeric impurities, and gave (10) as a colourless oil (920 mg, (92%), $[\alpha]_D^{25}$ −52° (*c* 0.94); $_{max.}$ ($CHCl_3$) 3 500 (OH), 1 710 (α,β-unsaturated ester); $\lambda_{max.}$ 212 (log ε 3.8); *m/z* (rel. int.) 334 $(M)^+$ (2%), and 83 $(C_5H_7O)^+$ (100%).

Cope Rearrangement of the Lactone (2).—The lactone (2) (1 g) was treated as above, giving a yellow oil, which, on the basis of t.l.c. and ^1H n.m.r. evidence, showed no trace of starting material. Filtration through a short pad of silica gel gave as a colourless oil (11 mg, yield 97%) (11), $[\alpha]_D^{25}$ −36° (*c* 0.91); $\nu_{max.}$ ($CHCl_3$) (no OH) band, 1 770 (γ-lactone), 1 710 (α,β-unsaturated ester), and 1 650 (double bonds); $\lambda_{max.}$ 215 (log ε 3.4); *m/z* (rel. int.) 332 $(M)^+$ (1%) and 84 (100%).

Epoxidation of Lactone (2).—A solution of the lactone (2) (100 mg, 0.30 mmol) in $CHCl_3$ (5 ml) was added *m*-chloroperbenzoic acid (MCPBA) (85%; 73 mg 0.36 mmol). The mixture was stirred for 10 min at room temperature, and then diluted with $CHCl_3$ (10 ml), washed with 5% aqueous $NaHCO_3$ (2 × 10 ml) and water (2 × 10 ml) and then dried ($MgSO_4$). Removal of the solvent gave a yellowish oil (100 mg) which was shown by ^1H n.m.r. spectroscopy to be a *ca.* 5 : 3 : 2 mixture of the epoxide (3) and the eudesmanolides (4) and (5). Alternatively the lactone (2) (100 mg) was added to a suspension of powdered NaOAc (100 mg) in $CHCl_3$ (10 ml) containing MCPBA (85%; 73 mg, 0.36 mmol). After being stirred for 20 min the suspension was treated as above to give the epoxide (3) (104 mg, 100%) as a colourless oil, $[\alpha]_D^{25}$ −36° (*c* 0.97), $\nu_{max.}$ ($CHCl_3$) (no OH), 1 770 (γ-lactone), 1 720 (α,β-unsaturated ester), and 1 650 (double bond); $\lambda_{max.}$ 215 (log ε : 3.4); *m/z* (rel. int.): 348 $(M)^+$ (1%) and 83 $(C_5H_7O)^+$ (100%).

Transannular Cyclization of the Epoxide (3).—Compound (3) (104 mg, 0.30 mmol) was dissolved in benzene (5 ml), and $BF_3{\cdot}Et_2O$ (10 μl) was added. Alternatively the same amount of the epoxide (3) was dissolved in ether (5 ml) and dilute. HCl (0.1 ml) added. After 30 min at room temperature, the mixture was diluted with $CHCl_3$ and washed with a 5% aqueous $NaHCO_3$ (2 × 5 ml) and water (2 × 5 ml) and dried ($MgSO_4$). Removal of the solvent gave a colourless oil (96 mg), which was shown by ^1H n.m.r. spectroscopy to be a *ca.* 3 : 2 mixture of the hydroxyeudesmanolides (4) and (5). Separation by preparative t.l.c. ($CHCl_3$–acetone, 6 : 1) gave (4) as a white powder (38 mg, yield 40%), m.p. 150 °C, $[\alpha]_D^{25}$ −20° (*c* 0.35); $\nu_{max.}$ (KBr) 3 500 (OH), 1 770 (γ-lactone), 1 710 (α,β-unsaturated ester); $\lambda_{max.}$ 215 (log ε 4); *m/z* (rel. int.): 348 $(M)^+$ (10%) and 83 $(C_5H_7O)^+$ (100%). The minor isomer (5) was obtained as a yellow oil, still containing (4) (*ca.* 15% as judged by its ^1H n.m.r. spectrum. The main features of the ^1H n.m.r. spectrum of (5) were, besides the resonance values of the angelate protons, as follows: δ($CDCl_3$)

Table 2. ^{13}C N.m.r. results determined at 50.3 (i) or 25.18 (ii) MHz with $SiMe_4$ as internal standard. Chemical shifts (δ) are expressed in p.p.m. Starred (*) assignments have been confirmed by selective proton decouplings. The other assignments are based upon multiplicities chemical shift considerations, and evaluation of the residual coupling constants in the single frequency off resonance decoupled spectra

Compound:	(1a,1b)[(I)] [a]	(2)[(I)] [a]		(4)[(II)] [a]	(8)[(II)] [a]
Solvent:	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	$CDCl_3$
C-1	130.5, 130.7 (d)	129.5 (d)	129.7 (d) *	75.11 (d)	197.2 (s)
C-2	29.96 (t)	25.62 (t)	25.86 (t)	32.27 (t)	38.76 (t) †
C-3	40.52, 40.65	39.48 (t)	39.52 (t)	122.2 (d) z	38.39 (t) †
C-4	134.3, 134.7 (s)	138.4 (s)	138.4 (s)	132.7 (s)	141.3 (s)
C-5	128.9, 126.9 (d)	123.2 (d)	124.1 (d) *	47.41 (d) †	121.6 (d)
C-6	75.12, 75.76 (d)	75.52 (d)	75.26 (d) *	77.34 (d)	74.75 (d)
C-7	53.80, 54.99 (d)	51.35 (d)	51.57 (d) *	47.01 (d) †	51.37 (d)
C-8	74.00, 74.79 (d)	72.24 (d)	73.15 (d) *	69.00 (d)	69.93 (d)
C-9	46.22, 46.62 (t)	43.65 (t)	43.75 (t) *	36.39 (t)	35.04 (t) †
C-10	135.4, 135.5 (s)	133.0 (s)	133.3 (s)	37.98 (s)	146.3 (s)
C-11	44.64, 44.65 (d)	38.63 (d)	39.01 (d)	37.13 (d)	38.40 (d)
C-12	99.56, 104.7 (d)	178.3 (s)	178.0 (s)	177.8 (s)	177.8 (s)
C-13	16.22, 16.73 (d)	16.99 (q)	17.03 (1) *	14.74 (q)	16.82 (q)
C-14	17.61, 17.82 (q)	16.99 (q)	17.19 (q) *	12.66 (q)	123.1(5)
C-15	16.31 (q)	20.87 (q)	20.42 (q) *	22.64 (q)	16.52 (q)

Compound:	(11)[(II)] [a]	(12)[(I)]	(17)[(I)]	(18)[(I)]	(19)[(II)]
Solvent:	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
C-1	146.6 (d)	147.1 (d)	130.8 (d)	131.8 (d)	134.4 (s)
C-2	111.7 (t) †	111.4 (t) †	24.23 (tβ †	24.15 (t) †	22.38 (t) †
C-3	115.1 (t) †	115.2 (t) †	46.75 (t) †	46.78 (t) †	45.45 (t) †
C-4	141.3 (s)	141.6 (s)	134.0 (s)	134.4 (s)	61.01 (s)
C-5	47.52 (d)	49.97 (s)	124.1 (d)	124.5 (d)	68.31 (d) ‡
C-6	77.14 (d)	77.86 (d)	75.85 (d) ‡	76.54 (d) ‡	75.31 (d) ‡
C-7	53.46 (d)	53.06 (d)	50.98 (d)	51.37 (d)	46.66 (d)
C-8	69.00 (d)	67.89 (d)	65.28 (d) ‡	55.11 (d) ‡	68.41 (d) ‡
C-9	38.17 (t)	41.86 (t)	36.86 (t) †	36.75 (t) †	36.54 (t) †
C-10	39.91 (s)	39.80 (s)	134.6 (s)	134.4 (s)	134.4 (s)
C-11	36.68 (d)	37.42 (d)	39.99 (d)	39.70 (d)	39.66 (d)
C-12	177.4 (s)	178.5 (s)	99.39 (d)	105.2 (d)	99.58 (d)
C-13	14.03 (q)	14.42 (q)	9.388 (q) *	9.044 (q)	9.283 (q)
C-14	20.15 (q)	21.20 (q)	16.48 (q)	16.50 (q)	16.40 (q)
C-15	24.64 (q)	24.52 (q)	17.43 (q)	17.38 (q)	18.17 (q)
				OCH_3 53.86 (q)	

[a] The ^{13}C signals for the angelate group were almost identical for all the compounds containing this group. Those observed in (2) are given as representative: δ($CDCl_3$) 166.4 (s, C-1′), 127.3 (s, C-2′), 138.8 (s, C-3′), 15.71 (q, C-4′), and 20.42 (q, C-5′); δ(C_6D_6) 166.5 (s, C-1′), 127.8 (s) C-2′), 138.9 (d, C-3′), 15.95 (q,* C-4′), and 20.92 (q,* C-5′).

† ‡ Assignments with the same sign in the same column are interchangeable.

5.20br (1 H, s, 8-H), 4.95br (1 H, s, 15_a-H), 4.83br (1 H, s, 15_b-H), 3.40 (1 H, dd, *J* 7.4 and 5.0 Hz, 1-H), 1.25 (3 H, d, *J* 7.5, 13-H), and 0.92 (3 H, s, 14-H); *m/z* (rel. int.): 348 $(M)^+$ (15%) and 83 $(C_5H_7O)^+$ (100%).

Photo-oxygenation of the Lactone (2).—A solution of (2) (300 mg) dissolved in methanol (20 ml) containing Rose Bengal (40 mg) or Methylene Blue (35 mg) was irradiated with a 700-W halogen lamp with introduction of oxygen and cooling. After 4 h the reaction mixture was worked up by evaporating the solvent, and the residue, dissolved into $CHCl_3$ (25 ml), was passed through a short column of silica gel 60 (70—230 mesh) to remove the dye. Evaporation of the solvent gave a brown oil, which was shown by ^1H n.m.r. spectroscopy to be a *ca.* 1 : 10 : 3 mixture of unchanged (2) and the hydroperoxides (6) and (7). Chromatography on a silica gel column ($CHCl_3$ as eluant) removed some coloured material and separated unchanged starting material from the mixture of hydroperoxides, which was obtained as a yellow oil (220 mg). Treatment of the mixture with Ac_2O (3 ml)–pyridine (1.5 ml) overnight gave a mixture of the α,β-unsaturated ketones (8) and (9) (180 mg), which displayed two slightly separated spots on t.l.c. ($CHCl_3$–acetone, 6 : 1). Separation of this mixture by preparative layer chromotography, (methanol–water, 75 : 25) gave pure (8) (80 mg), which was crystallized from ethyl acetate to give shining needles of m.p. 125 °C, $[\alpha]_D^{25}$ −152° (*c* 0.25); $\nu_{max.}$ (KBr) no hydroxy band, 1 780 (γ-lactone), 1 710 (α,β-unsaturated ester), 1 670 (α,β-unsaturated ketone); $\lambda_{max.}$ 215 (log ε 3.8) *m/z* (rel. int.): 346 $(M)^+$ (1%) and 83 $(C_5H_7O)^+$ (100%). Compound (9) was obtained as a very unstable yellow oil, the ^1H n.m.r. spectrum of which showed it not to be completely pure. Further attempted purification resulted in extensive decomposition of the sample. The ^1H n.m.r. spectrum (δ 5.90 (1 H, t, *J* 11 Hz, 8-H), 5.30br (1 H, d, *J* 11 Hz, 9-H), 5.15 (1 H, d, *J* 9 Hz. 5-H), 1.80br (3 H, s, 14-H), 1.60br (3 H, s, 15-H), and 1.20 (3 H, d, *J* 7 Hz, 13-H) is in keeping with structure (9).

Saponification of the Lactone (2).—The lactone (2) (200 mg) was dissolved in 5% methanolic KOH (10 ml); after 7 days the solution was diluted with water (30 ml) and neutralized with 1% HCl. Extraction with $CHCl_3$ gave a yellow oil, which, when analysed by t.l.c. ($CHCl_3$–acetone, 6 : 1) showed the presence of several compounds. Separation by preparative t.l.c. using the same eluant as above afforded uncharged (2) (56 mg) and a pure (t.l.c.) yellow oil (32 mg), the ^1H n.m.r.

spectrum of which revealed the presence of a major compound. Attempted oxidation of this compound with PCC resulted in its destruction.

Saponification of the Lactone (11).—Compound (11) (500 mg) was saponified as above, to give after 7 days a thick oil, which was separated by column chromatography on silica gel. Fractions eluted with $CHCl_3$ afforded starting material (160 mg); the ones eluted with $CHCl_3$–methanol (9 : 1) gave the hydroxyelemanolide (12) (151 mg, 40%), m.p. 94 °C, $[\alpha]_D^{25}$ −25 (*c* 0.66), $\nu_{max.}$ (KBr) 3 400 (OH) and 1 770 (γ-lactone); no u.v. absorption above 210 nm; *m/z* (rel. int.) 250 $(M)^+$ (1%) and 100 (100%).

Oxidation of the Hydroxylactone (12).—Compound (12) (160 mg, 0.60 mmol) were oxidized with pyridinium chlorochromate (PCC) (171 mg, 0.80 mmol) in the presence of powdered NaOAc (8.29 mg, 0.1 mmol) as described for compound (1). Compound (14) (130 mg) was obtained as a white powder, m.p. 102—105 °C, $[\alpha]_D^{25}$ +90° (*c* 0.46); $\nu_{max.}$ (KBr) (no OH), 1 770 (γ-lactone), and 1 770 (ketone); *m/z* (rel. int.): 148 $(M)^+$ (1%), and 69 (100%).

Keto-acid (15).—A sample of (14) (100 mg) was adsorbed on a preparative t.l.c. plate and left for 2 days. Elution with $CHCl_3$–methanol (9 : 1) gave the keto-acid (15) quantitatively as a colourless oil, $[\alpha]_D^{25}$ +128° (*c* 1.8); $\nu_{max.}$ ($CHCl_3$) 3 500—2 750br band, CO_2H) 1 710 (CO_2H), and 1 675 (α,β-unsaturated ketone); *m/z* (rel. int.) 248 $(M)^+$ (6%). Methylation with an excess of diazomethane gave an oily methyl ester of $[\alpha]_D^{25}$ +140° (*c* 0.41); $\nu_{max.}$ ($CHCl_3$) (no OH), 1 735 (ester), and 1 675 (α,β-unsaturated ketone); *m/z* (rel. int.): 262 $(M)^+$ (3%) and 163 (100%).

Saponification of (10).—A sample of (10) (500 mg) was dissolved in methanolic KOH (25 ml). The reaction was followed by t.l.c. ($CHCl_3$–acetone, 6 : 1), and after 60 h all of (10) had reacted. The solution was diluted with water (50 ml) and extracted with $CHCl_3$ (3 × 20 ml). The organic phase was washed with water and dried. Evaporation of the solvent gave a yellow oil (400 mg), which was chromatographed on a column of silica gel; fractions eluted with $CHCl_3$–methanol (5 : 2) gave (16) as a white powder (330 mg), m.p. 98—100 °C $[\alpha]_D^{25}$ −5.8° (*c* 0.51); $\nu_{max.}$ (KBr) 3 310, 3 115 (OH), and 1 640 and 1 635 (double bonds); no u.v. absorption above 210 nm; *m/z* (rel. int.): 252 $(M)^+$ (2%) and 93 (100%).

Oxidation of (16) *to the Keto-lactone* (14).—Compound (16) (67 mg, 0.26, mmol) was oxidized with PCC (217 mg, 1 mmol) in the presence of powdered NaOAc (24.7 mg, 0.3 mmol) as described for compound (1). Compound (14) was obtained (37 mg, 54%).

Saponification of Hallerin.—Compound (1) (1.340 g, 4.0 mmol) was dissolved in 5% methanolic KOH (65 ml). After 14 h all of (1) had reacted. The solution was diluted with water (120 ml) and extracted with $CHCl_3$ (3 × 60 ml). The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give a solid residue (894 mg). Crystallization from Et_2O afforded pure (17) (475 mg, 47%). Chromatography of the mother liquors and crystallization from ether gave a further crop of (17) (85 mg); ^{13}C n.m.r. analysis of the mother liquors from the second crop of (17) showed that they contained uncrystallized (17) with no trace of its C-12 epimer. Large crystals of (17) were obtained from ethyl acetate–ether. Acidification of the reaction mixture, after previous extraction with $CHCl_3$, and extraction of the acid solution with $CHCl_3$ afforded only gummy red material (108 mg) which contained no major compound. Compound (17) had m.p. 149—150 °C, $[\alpha]_D^{25}$ −64° (*c* 1.20), $\nu_{max.}$ (KBr) 3 360, 3 280 (OH), and 1 660 and 1 655 (double bonds); *m/z* (rel. int.): 252.1707 ($C_{15}H_{24}O_3$ requires 252.1725) $(M)^+$ (2%), 83 (100%).

Methylation of the Lactol (17).—The lactol (17) (150 mg, 0.59 mmol) was dissolved in CH_2Cl_2 (2 ml) and the solution stirred with CH_3I (750 μl) and Ag_2O (480 mg) for 4 h at room temp. After filtration, the reaction mixture was evaporated to afford (18) (162 mg, 96%), which crystallized from ether, m.p. 130 °C, $[\alpha]_D^{25}$ −115° (*c* 0.57); $\nu_{max.}$ (KBr) 3 440 (OH), and 1 660 and 1 615 (double bonds); *m/z* (rel. int.): 266 $(M)^+$ (1%) and 83 (100%).

Epoxidation of the Lactol 17.—(a) *With* 1 *equiv. of MCPBA.* The lactol (17) (100 mg, 0.40 mmol) was added to a suspension of powdered NaOAc (100 mg) in $CHCl_3$ (3 ml) containing MCPBA (85%; 95.5 mg, 0.46 mmol). After being stirred for 3 h at room temperature, the mixture was diluted with $CHCl_3$ (10 ml), washed with 5% aqueous $NaHCO_3$ (2 × 10 ml) and water (2 × 10 ml) and then dried ($MgSO_4$). Removal of the solvent gave (19) (102 mg, 92%), which crystallized from ethyl acetate; it had m.p. 207—209°, $[\alpha]_D^{25}$ +31 (*c* 0.98); $\nu_{max.}$ (KBr) 3 300 (OH) and, 1 665 (double bond); *m/z* (rel. int.) 268 $(M)^+$ (1%) and, 83 (100%).

(b) *With* 2 *equiv. of MCPBA.* The lactol (17) (100 mg, 0.40 mmol) were epoxidized with MCPBA (85%; 194 mg, 0.95 mmol) as described above for 16 h. Work-up as above gave (20) (110 mg, 97%) as a white powder, m.p. 218—220 °C (decomp.), $[\alpha]_D^{25}$ −53° (pyridine, *c* 0.48); $\nu_{max.}$ (KBr) 3 300 (OH), no double bond absorption in the range 1 700—1 600; *m/z* (rel. int.): 284 $(M)^+$ (0.4%) and 125 (100%).

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References

1 M. Holub, Z. Samek, V. Herout, and F. Šorm, *Collect. Czech. Chem. Commun.*, 1967, **32**, 591.
2 M. Holub, Z. Samek, S. Vašíčková, and M. Masojídková, *Collect. Czech. Chem. Commun.*, 1978, **43**, 2444.
3 G. Appendino, F. Belliardo, G. M. Nano, and S. Stefenelli, *J. Agric. Food. Chem.*, 1982, **30**, 518.
4 M. Novotny, Z. Samek, and F. Šorm, *Collect. Czech. Chem. Commun.*, 1966, **31**, 371.
5 R. R. Fraser, *Can. J. Chem.*, 1960, **38**, 549.
6 G. C. Levy, R. L. Lichter, and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance Spectroscopy,' Wiley and Sons, New York, 1980, pp. 282—287.
7 R. W. Doskotch, E. H. Fairchild, C. T. Huang, J. H. Wilton, M. A. Beno, and G. G. Christoph, *J. Org. Chem.*, 1980, **45**, 1441.
8 Z. Samek and J. Harmatha, *Collect. Czech. Chem. Commun.*, 1978, **43**, 2779.
9 J. B. Hendrickson, *Tetrahedron*, 1963, **19**, 1387.
10 Z. Samek, M. Holub, U. Rychlewska, H. Grabarczyk, and B. Drozdz, *Tetrahedron Lett.*, 1979, 2691.
11 W. Herz, S. V. Govindan, and J. F. Blount, *J. Org. Chem.*, 1980, **45**, 1113.

12 C. R. Narayanan and N. K. Venkatasubramanian, *J. Org. Chem.*, 1968, **34**, 229.
13 P. S. Pregosin, E. W. Randall, and T. B. H. McMurry, *J. Chem. Soc., Perkin Trans. 1*, 1972, 299.
14 M. R. Lindley, N. A. B. Gray, D. H. Smith, and C. Djerassi, *J. Org. Chem.*, 1982, **47**, 1027 and references cited here.
15 N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, 1974, **8**, 1.
16 N. H. Fischer, E. J. Oliver, and H. D. Fischer, in ' Progress in the Chemistry of Organic Natural Products,' ed. W. Herz, H. Grisebach and G. W. Kirby, Springer-Verlag, Wien, New York, 1979, pp. 189—190.
17 K. Takeda, *Tetrahedron*, 1974, **30**, 1525.
18 Z. Samek, *Collect. Czech. Chem. Commun.*, 1978, **43**, 3210.
19 V. G. S. Box, W. R. Chan, and D. R. Taylor, *Tetrahedron Lett.*, 1971, 4371.
20 M. Holub, M. Buděšísnský, Z. Smitalová, D. Šaman, and U. Rychlewska, *Tetrahedron Lett.*, 1982, 4853.
21 For a recent review on the mechanism of the ene reaction, see: L. M. Stephenson, M. J. Grdina, and M. Orfanopulos, *Acc. Chem. Res.*, 1980, **13**, 419.
22 (*a*) B. Drozdz, M. Holub, Z. Samek, V. Herout, and F. Šorm, *Collect. Czech. Chem. Commun.*, 1968, **33**, 1730; (*b*) H. Yoshioka, W. Renold, and T. J. Mabry, *Chem. Commun.*, 1970, 148.
23 Z. Samek and M. Buděšínský, *Collect. Czech. Chem. Commun.*, 1979, **44**, 558.
24 R. Neher, in ' Steroid Chromatography,' Elsevier Publishing Co., New York, 1964, p. 125.
25 M. Calleri, G. Chiari, and D. Viterbo, following paper.

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