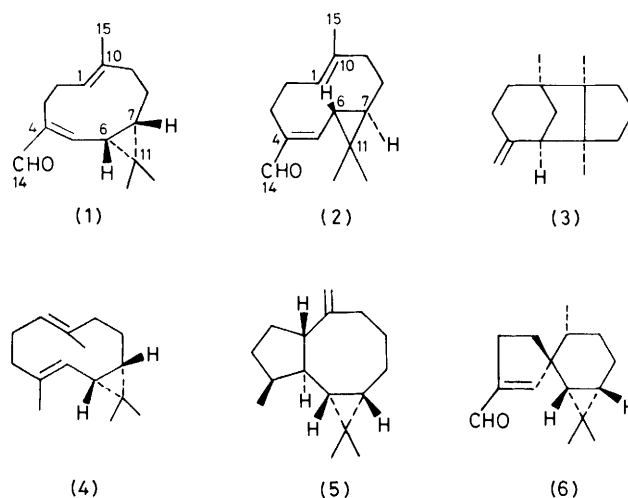# Structures and Conformations of (—)-Isobicyclogermacrenal and (—)-Lepidozenal, Two Key Sesquiterpenoids of the *cis*- and *trans*-10,3-Bicyclic Ring Systems, from the Liverwort *Lepidozia vitrea*: *X*-Ray Crystal Structure Analysis of the Hydroxy Derivative of (—)-Isobicyclogermacrenal

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The structures and absolute configurations of the two sesquiterpene aldehydes, (—)-isobicyclogermacrenal (1) and (—)-lepidozenal (2), which were isolated from the liverwort *Lepidozia vitrea*, have been determined on the basis of chemical and spectroscopic evidence to be (6*R*,7*S*)-6,11-cyclogermacra-1(10)-*E*,4*E*-dien-14-al and (6*R*,7*R*)-lepidoza-1(10)*E*,4*E*-dien-14-al, consisting of the *cis*- and *trans*-10,3-bicyclic ring systems. The structure of the former (1) has been confirmed by a single-crystal *X*-ray analysis of its hydroxy derivative (7). The molecular conformations, biogenetical features, and biological activity are also described.

Liverworts (Hepaticae) are placed in a special group, considered as an early stage of the evolution of terrestrial plants. They contain several oil bodies, characteristic of the species, in each cell of the gametophytes. These unique plants generally elaborate the enantiomeric (*ent*) type sesquiterpenoids, corresponding to the antipodal structures of those in higher plants, as one of the most important biochemical features.[1] In previous papers,[2] we have reported the isolation and structural elucidation of a series of acetyl hemiacetals with the novel *ent*-2,3-seco-alloaromadendrane carbon skeleton from the liverwort *Plagiochila semidecurrens*. These sesquiterpenoids inhibit the growth of the leaves and roots of rice seedlings[3] and act as allomones in ecological systems.[4] Recently, we furthermore isolated two kinds of sesquiterpene aldehydes having plant-growth-inhibitory activity from the other leafy liverwort *Lepidozia vitrea* Steph. belonging to the Lepidoziaceae of the Jungermanniales. The structures including the absolute configurations of the two biologically active sesquiterpenoids named (—)-isobicyclogermacrenal and (—)-lepidozenal were, respectively, determined by the following chemical and spectral evidence to be *ent*-isobicyclogermacren-14-al, or (6*R*,7*S*)-6,11-cyclogermacra-1(10)*E*,4*E*-dien-14-al (1) † and (6*R*,7*R*)-lepidoza-1(10)*E*,4*E*-dien-14-al (2),‡ consisting of the *cis*- and *trans*-10,3-bicyclic ring systems. The structure of the former (1) was confirmed by single crystal *X*-ray analysis of its hydroxy derivative (7). In this paper we present the details for determining the molecular structures and conformations as well as the biogenetical considerations and the biological activity of the two new sesquiterpenoids.[5] These sesquiterpene aldehydes, (—)-isobicyclogermacrenal (1) and (—)-lepidozenal (2), were isolated from a methanol extract of the liverwort by a combination of column chromatography and preparative layer chromatography (p.l.c.) over silica gel. The three *ent* type sesquiterpene hydrocarbons, (—)-β-pompene (3)[6] [syn. (—)-gymnomitrene[7]], (—)-*ent*-bicyclogermacrene (4),[2a,8] and (—)-*ent*-aromadendrene (5),[9] were also obtained from the extract together with the third sesquiter-

pene aldehyde, (+)-vitrenal (6); the results from the last compound are described in the following paper.[10]

Structure of (—)-*Isobicyclogermacrenal* (1).—The first compound (—)-isobicyclogermacrenal (1), $C_{15}H_{22}O$, $[\alpha]_D$ —168°, was revealed by the following spectroscopic evidence to be a bicyclic sesquiterpenoid which contained as partial structures a formyl group conjugated with a trisubstituted double bond [$\lambda_{max.}$ 261 nm; $\nu_{max.}$ 2 810, 2 705, 1 685, and 1 624 cm⁻¹; δ 6.28 (1 H, d, *J* 9.0 Hz) and 9.25 (1 H, s)] as well as another trisubstituted double bond bearing a methyl group [$\nu_{max.}$ 863 cm⁻¹; δ 1.25 (3 H, d, *J* 1.5 Hz) and 5.06 (1 H, m)] and a cyclopropane ring with a *gem*-dimethyl group [$\nu_{max.}$ 1 382 and 1 377 cm⁻¹; δ 0.1—1.1 (2 H, m) and 1.18 and 1.21 (each 3 H, s)]. Indeed, the aldehyde (1) was reduced to a hydroxy derivative (7), $C_{15}H_{24}O$ ($\nu_{max.}$ 3 620 and 3 385 cm⁻¹), by reaction with lithium aluminium hydride (Scheme 1). The alcohol (7), which regenerated the original aldehyde (1) by oxidation with manganese dioxide, produced a monoepoxide (8), $C_{15}H_{24}O_2$ [$\nu_{max.}$ 3 550, 3 525, and 3 450 cm⁻¹], leaving the allylic alcohol moiety. Moreover, the off-resonance ¹³C n.m.r. spectrum of the alcohol (7) gave 3 singlets, 4 doublets, 5 triplets, and 3 quartets indicating the bicyclic framework and the partial structures. The patterns of the ¹H n.m.r. spectra of the aldehyde (1) and the alcohol (7),

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† The numbering used throughout for this ring system differs from that prescribed by the IUPAC authorities in that the 14 and 15 sites are reversed. This has been allowed for consistency with earlier published work.

‡ We propose the name lepidozane for the new *trans*-fused 10,3-bicyclic ring system and suggest the numbering shown in the formula (2).
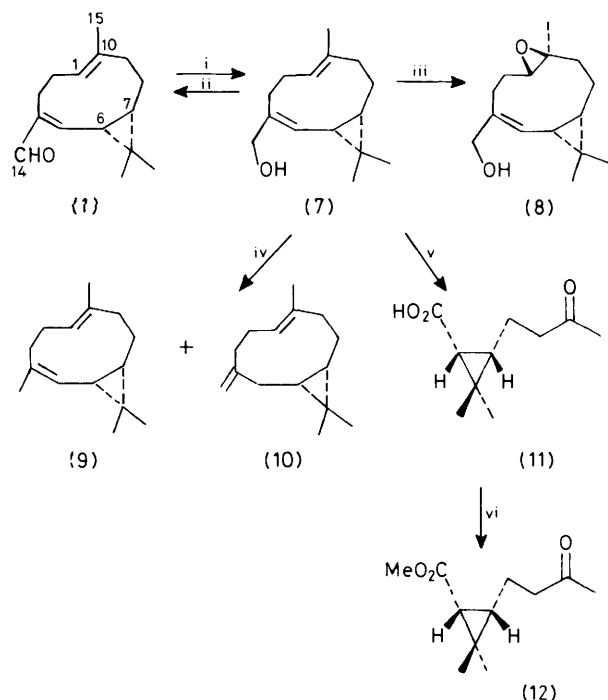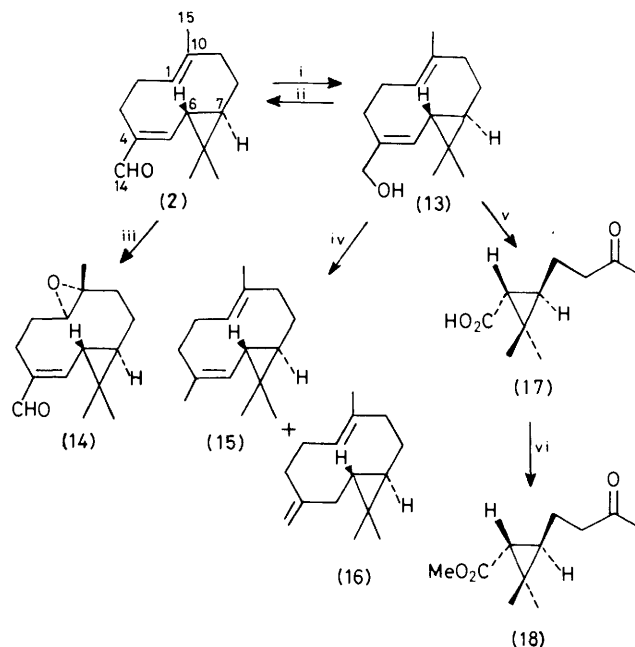
Scheme 1. *Reagents:* i, LiAlH$_4$; ii, MnO$_2$; iii, *m*-ClC$_6$H$_4$CO$_3$H; iv, C$_5$H$_5$N–SO$_3$, LiAlH$_4$; v, O$_3$, H$_2$O$_2$; vi, CH$_2$N$_2$

Scheme 2. *Reagents:* i, LiAlH$_4$; ii, MnO$_2$; iii, *m*-ClC$_6$H$_4$CO$_3$H; iv, C$_5$H$_5$N–SO$_3$, LiAlH$_4$; v, O$_3$, H$_2$O$_2$; vi, CH$_2$N$_2$

apart from the signals of formyl and hydroxy groups, were analogous to those of the known sesquiterpene hydrocarbons, bicyclogermacrene and isobicyclogermacrene, being the *trans*, *trans*- and *trans,cis*-cyclodeca-1,5-diene with a *gem*-dimethyl cyclopropane ring by *cis*-fusion, respectively.[8,11] When the alcohol (7) was treated with pyridine–sulphur trioxide complex in ether followed by lithium aluminium hydride [12] it was reduced to a polar hydrocarbon (9), C$_{15}$H$_{24}$ [δ 1.42 and 1.72 (each 3 H, d, *J* 1.5 Hz)], and a less polar hydrocarbon (10), C$_{15}$H$_{24}$ [δ 1.66 (3 H, d, *J* 1.5 Hz) and 4.83 (2 H, br s)], having an isomerized exocyclic double bond, in a ratio of 2 : 1. The major sesquiterpene hydrocarbon (9) was identified as isobicyclogermacrene, excluding the absolute configuration,* by coincidence of the i.r. and [1]H n.m.r. spectra with those of the authentic specimen prepared by isomerization of the natural (+)-bicyclogermacrene (25), an enantiomer of (−)-*ent*-bicyclogermacrene (4).[11] The geometries of the two double bonds were alternatively shown to be C(1)–C(10) *trans* and C(4)–C(5) *cis* on the basis of n.O.e. experiments on the original aldehyde (1): when the signal of the formyl proton (δ 9.25) was saturated by double irradiation, the integrated intensity of the 5-H signal (δ 6.28) increased and the value was measured as *ca.* 14%. However, saturation of the 10-methyl (δ 1.25) caused no increase in intensity of the 1-H signal (δ 5.06).

In order to establish the absolute configuration of the aldehyde (1), the alcohol (7) was subjected to ozonolysis in ethyl acetate and the resulting ozonide was oxidatively decomposed with hydrogen peroxide to yield an acid (11), C$_{10}$H$_{16}$O$_3$ (ν$_{max.}$ 3 500—2 500 and 1 725 cm^{-1}), which was then converted into a methyl ester (12), C$_{11}$H$_{18}$O$_3$ (ν$_{max.}$ 1 730 cm^{-1}). The spectroscopic properties and the signs of the specific optical rotations of both compounds, (11) and (12), were, respectively, identical with those of the corresponding *cis*-keto acid and *cis*-keto

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* The optical rotation of the authentic isobicyclogermacrene prepared from (+)-bicyclogermacrene was not reported, but it should have the opposite configuration.

ester derived from (−)-taylorione, *ent*-1,10-seco-aromadendra-1(5),4(15)-dien-10-one.[1b] Accordingly, the structure and absolute configuration of (−)-isobicyclogermacrenal should be represented by *ent*-isobicyclogermacren-14-al, or (6*R*,7*S*)-6,11-cyclogermacra-1(10)*E*,4*E*-dien-14-al (1). This compound is the first example of the naturally occurring isobicyclogermacrene sesquiterpenoid.

Structure of (−)-*Lepidozenal.*—The second aldehyde (2), C$_{15}$H$_{22}$O, [α]$_D$ −169°, was characterized by spectroscopic methods as a 10,3-bicyclic sesquiterpenoid containing a *gem*-dimethyl cyclopropane ring [δ 0.4—1.3 (2 H, m) and 1.15 and 1.25 (each 3 H, s)] and a formyl group conjugated with a tri-substituted double bond [λ$_{max.}$ 265 nm; ν$_{max.}$ 1 685 and 1 630 cm^{-1}; δ 6.33 (1 H, d, *J* 10.0 Hz) and 9.30 (1 H, s)] along with another trisubstituted double bond with a methyl group [ν$_{max.}$ 870 cm^{-1}; δ 1.64 (3 H, d, *J* 1.5 Hz) and 5.05 (1 H, m)]. A close similarity between the spectral properties of the first aldehyde (1) and those of the second (2) suggested that the two were stereoisomers with respect to one of the three geometries on the two double bonds and one cyclopropane ring existing in both the molecules of cyclodeca-1,5-diene fused with a cyclopropane. Therefore, similar reactions to those applied to the first compound were applied to this compound (Scheme 2): the aldehyde (2) was reduced with lithium aluminium hydride to afford an allylic primary alcohol (13), C$_{15}$H$_{24}$O (ν$_{max.}$ 3 610 and 3 350 cm^{-1}), which was oxidized by treatment with manganese dioxide to give the original compound (2). The aldehyde (2) also produced a monoepoxide (14), C$_{15}$H$_{22}$O$_2$ [ν$_{max.}$ 1 685 and 1 632 cm^{-1}; δ 6.41 (1 H, d, *J* 10.0 Hz) and 9.33 (1 H, s)], leaving the α,β-unsaturated aldehyde. Furthermore, the pyridine–sulphur trioxide–lithium aluminium hydride reduction sequence [12] gave a new sesquiterpene hydrocarbon (15), C$_{15}$H$_{24}$ [δ 1.63 and 1.76 (each 3 H, d, *J* 1.5 Hz)], along with its double bond isomer (16), C$_{15}$H$_{24}$ [δ 1.54 (3 H, d, *J* 1.5 Hz) and 4.83 (2 H, br s)], in the ratio 5 : 1. The major hydrocarbon, (−)-lepidozene, showed different spectra from not only those of isobicyclogermacrene but also those of bicyclogermacrene.[8,11] In the cyclodecadiene molecule the geometries

of the two double bonds were then clarified as C(1)–C(10) *trans* and C(4)–C(5) *cis* by the ^{13}C n.m.r. chemical shifts of 10-methyl (δ 15.5) of the alcohol (13) and of 10-methyl (δ 15.5) and 4-methyl (δ 24.1) of the hydrocarbon (15).[13,14] The *trans* and *cis* geometries of the cyclodeca-1,5-diene structure were also supported on the basis of n.O.e. experiments on the original aldehyde (2): the integrated intensity of the 5-H (δ 6.33) signal increased *ca.* 16% when the formyl proton (δ 9.30) was saturated by double irradiation. The saturation of the 10-methyl (δ 1.64), however, caused no increase in intensity of the 1-H signal (δ 5.05). From these results the stereostructure of (−)-lepidozenal (2) should be a novel *trans*-fused 10,3-bicyclic ring system having the *trans,cis*-1,5-diene moiety. In addition, the alcohol (13) was subjected to ozonolysis to give a keto acid (17), $C_{10}H_{16}O_3$ (ν_{max} 3 500—2 500 and 1 715 cm^{-1}), which was then converted into a methyl ester (18), $C_{11}H_{18}O_3$ (ν_{max} 1 730 cm^{-1}). In the ^{1}H n.m.r. spectrum of the latter upon addition of the shift reagent Eu(fod)$_3$ (0.25 molar equiv.) the cyclopropane proton adjacent to the methoxy-carbonyl group resonated at δ 2.33 with a coupling constant of 5.5 Hz; this contrasted with the value (*J* 8.0 Hz) of the *cis*-keto ester (12) derived from (−)-isobicyclogermacrenol (7). The difference defined the *trans*-orientation of the two sub-stituents on the *gem*-dimethyl cyclopropane ring.[15,16] Further-more, both ^{13}C n.m.r. spectra of the *trans*- (18) and *cis*-keto ester (12) were, respectively, correlative to those of the methyl esters of *trans*- and *cis*-chrysanthemic acid as shown in Figure 1.[17]

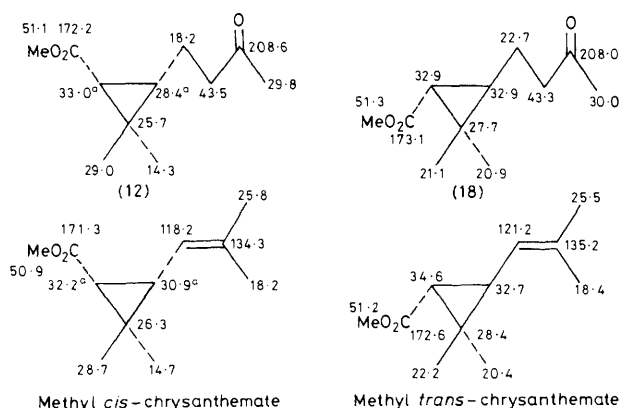Establishment of the absolute configuration was performed

Figure 1. Comparison of ^{13}C n.m.r. chemical shifts of the *cis*-keto ester (12) and *trans*-keto ester (18) with those of the corresponding methyl *cis*-chrysanthemate and methyl *trans*-chrysanthemate [17]

by correlation of (−)-*trans*-keto acid (17) and (−)-*trans*-keto ester (18) with the corresponding compounds prepared from (+)-methyl *trans*-chrysanthemate (19) (Scheme 3); the (+)-*trans*-ester (19) $C_{11}H_{18}O_2$, which was obtained by methanolysis of (+)-β-allethrin,[18] was degraded by ozonolysis to an alde-hyde (20), $C_8H_{12}O_3$ (ν_{max} 1 730 and 1 710 cm^{-1}). It was then subjected to a Wittig reaction with 2-oxopropylidenetriphenyl-phosphorane to afford two kinds of the keto esters (21), $C_{11}H_{16}O_3$ [δ 6.20 (1 H, d, *J* 15.5 Hz) and 6.55 (1 H, dd, *J* 15.5 and 7.5 Hz)], and (22), $C_{11}H_{16}O_3$ [δ 5.68 (1 H, dd, *J* 11.5 and 9.5 Hz) and 6.23 (1 H, d, *J* 11.5 Hz)], containing *trans*- and *cis*-double bonds in a ratio of 7 : 1. The major compound (21) was hydrogenated to produce the (−)-*trans*-keto ester (18), $C_{11}H_{18}O_3$, which was, furthermore, hydrolysed to the (−)-*trans*-keto acid (17), $C_{10}H_{16}O_3$. The spectral data and the signs of optical rotations of both the keto acid (17) and the keto ester (18) derived from (−)-lepidozenal (2) were coincident, respectively, with those of (−)-*trans*-keto acid (17) and (−)-*trans*-keto ester (18) prepared from (+)-methyl *trans*-chrys-anthemate (19).

The structure including the absolute configuration of (−)-lepidozenal was, therefore, determined as (6R,7R)-lepidoza-1(10)E,4E-dien-14-al (2). This is the first sesquiterpenoid having a *trans*-fused 10,3-bicyclic ring system, although an example of a diterpenoid containing an additional isoprene unit on the same *trans* system has been reported.[19]

X-Ray Crystal Analysis of the Hydroxy Derivative of (−)-Isobicyclogermacrenal, and Conformational and Biogenetic Characteristics of the Two New Sesquiterpenoids.—In order to confirm the proposed structure of (−)-isobicyclogermacrenal (1) and to determine the molecular conformation, we undertook the X-ray analysis of the hydroxy derivative, (+)-isobicyclogermacrenol (7); this was the first analysis of bicyclogermacrene type compounds.

The final positional parameters for non-hydrogen atoms and for hydrogen atoms are, respectively, given in Tables 1 and 2. Absolute configurations of the two crystallographically in-dependent molecules are illustrated in Figure 2. The two in-dependent molecules have the same chirality and almost identical conformation. Thus, the structure of the original (−)-isobicyclogermacrenal is in accord with that proposed on the basis of the chemical and spectral evidence, and is represented by the stereostructure (1) consisting of the *cis*-10,3-bicyclic ring system with the *trans,cis*-1,5-diene unit, *i.e.* an isobicyclo-germacrene structure.

Bond lengths and bond angles of the alcohol (7) are listed in Table 3 along with their standard deviations, and selected torsion angles are summarized in Table 4. In these cases,
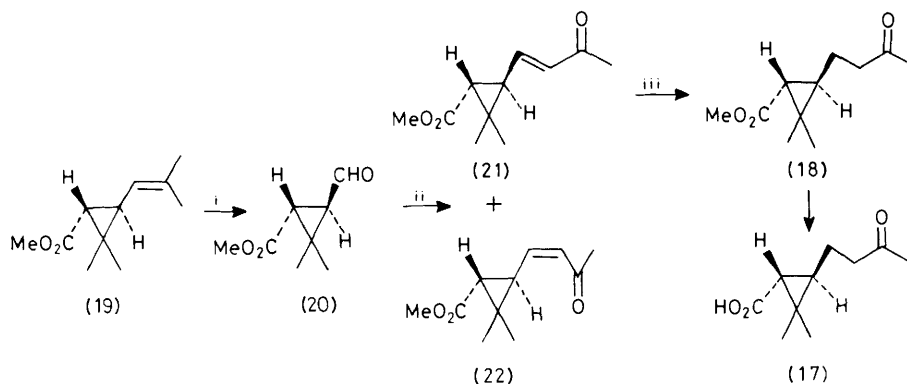
Scheme 3. *Reagents:* i, O$_3$, Zn–CH$_3$CO$_2$H; ii, (C$_6$H$_5$)$_3$P=CHCOCH$_3$; iii, H$_2$–PtO$_2$

Table 1. Fractional co-ordinates ($\times 10^4$) for non-hydrogen atoms, with estimated standard deviations in parentheses

Atom	x	y	z
(a) Molecule (A)			
O	$-659(7)$	7 404(3)	9 435(2)
C(1)	4 207(12)	8 743(4)	8 181(3)
C(2)	3 596(12)	8 834(4)	8 733(3)
C(3)	3 418(9)	8 011(3)	8 987(2)
C(4)	1 777(7)	7 510(3)	8 733(2)
C(5)	2 163(8)	7 012(3)	8 352(2)
C(6)	4 215(8)	6 837(3)	8 124(2)
C(7)	4 759(9)	7 063(3)	7 569(2)
C(8)	3 365(13)	7 520(4)	7 221(2)
C(9)	3 724(16)	8 416(5)	7 270(3)
C(10)	2 976(11)	8 716(4)	7 782(3)
C(11)	4 551(9)	6 201(3)	7 711(2)
C(12)	6 514(11)	5 718(3)	7 757(2)
C(13)	2 740(11)	5 742(3)	7 517(2)
C(14)	$-406(9)$	7 649(4)	8 911(2)
C(15)	695(12)	8 886(4)	7 792(3)
(b) Molecule (B)			
O	1 824(6)	6 579(2)	10 059(2)
C(1)	6 797(11)	4 680(4)	9 197(2)
C(2)	6 233(11)	5 539(4)	9 156(2)
C(3)	5 940(9)	5 900(3)	9 695(2)
C(4)	4 247(8)	5 497(3)	9 993(2)
C(5)	4 520(8)	4 888(3)	10 304(2)
C(6)	6 534(8)	4 524(3)	10 441(2)
C(7)	7 190(9)	3 695(3)	10 280(2)
C(8)	5 864(13)	3 173(4)	9 944(3)
C(9)	6 329(15)	3 285(4)	9 368(3)
C(10)	5 574(12)	4 065(4)	9 176(2)
C(11)	6 795(10)	3 878(3)	10 840(2)
C(12)	8 613(14)	3 930(4)	11 182(2)
C(13)	4 871(13)	3 520(4)	11 088(3)
C(14)	2 081(9)	5 790(3)	9 879(2)
C(15)	3 317(13)	4 189(4)	9 021(3)

Table 2. Hydrogen atom fractional co-ordinates ($\times 10^3$) and isotropic parameters with standard deviations, labelled according to their bonded carbon atoms

	x	y	z	B
(a) Molecule (A)				
OH	123(10)	772(3)	958(2)	5.1(18)
H(1)	551(11)	872(4)	809(3)	9.0(22)
H(2a)	409(20)	925(6)	891(4)	15.6(43)
H(2b)	214(10)	908(4)	879(2)	6.0(15)
H(3a)	297(7)	811(2)	933(1)	2.1(8)
H(3b)	489(9)	771(3)	899(2)	5.6(14)
H(5)	112(7)	676(2)	820(1)	2.2(9)
H(6)	542(8)	688(3)	834(2)	4.1(11)
H(7)	604(7)	718(3)	755(2)	2.3(10)
H(8a)	185(9)	737(3)	733(2)	4.9(13)
H(8b)	342(9)	734(3)	690(2)	5.1(13)
H(9a)	310(11)	866(4)	700(2)	8.0(18)
H(9b)	521(10)	850(4)	720(2)	7.2(19)
H(14a)	$-160(10)$	739(3)	872(2)	7.2(16)
H(14b)	$-88(8)$	825(3)	889(2)	4.2(11)
H(12a) *	657	546	738	5.0
H(12b) *	680	524	797	5.0
H(12c) *	744	605	793	5.0
H(13a) *	325	539	723	5.0
H(13b) *	243	520	774	5.0
H(13c) *	163	615	748	5.0
H(15a) *	40	37	785	5.0
H(15b) *	34	926	808	5.0
H(15c) *	21	913	746	5.0
(b) Molecule (B)				
OH	102(12)	683(4)	989(3)	8.5(22)
H(1)	816(8)	456(3)	929(2)	4.0(11)
H(2a)	487(8)	555(3)	896(2)	4.6(12)
H(2b)	734(10)	585(3)	896(2)	6.7(17)
H(3a)	538(9)	650(3)	968(2)	5.6(13)
H(3b)	741(8)	583(3)	989(2)	4.4(12)
H(5)	354(9)	462(3)	1 042(2)	4.8(15)
H(6)	760(7)	488(2)	1 043(1)	1.8(8)
H(7)	888(8)	361(3)	1 019(2)	4.0(11)
H(8a)	608(11)	260(4)	1 005(3)	7.2(16)
H(8b)	452(10)	329(3)	1 000(2)	5.3(15)
H(9a)	581(10)	285(3)	924(2)	5.5(15)
H(9b)	790(13)	317(4)	927(3)	10.2(24)
H(14a)	175(7)	571(2)	952(2)	3.0(9)
H(14b)	103(10)	541(3)	1 007(2)	6.6(15)
H(12a) *	922	342	1 132	5.0
H(12b) *	985	419	1 099	5.0
H(12c) *	834	428	1 149	5.0
H(13a) *	399	336	1 079	5.0
H(13b) *	540	303	1 126	5.0
H(13c) *	379	376	1 136	5.0
H(15a) *	218	384	933	5.0
H(15b) *	318	375	864	5.0
H(15c) *	282	467	898	5.0

* These positions are fixed.

the values for the two molecules in the asymmetric unit are labelled A and B, and those of the latter are given in square brackets in the subsequent discussion. The mean lengths of C–C bonds in the cyclodecadiene ring {C(sp^3) 1.526 [1.526], C(sp^3)–C(sp^2) 1.483 [1.495], C(sp^2)–C(sp^2) 1.313 Å [1.314 Å]} are comparable with the expected values, although a comparison of individual bond lengths is not warranted. The mean bond length in the cyclopropane ring {1.523 Å [1.514 Å]}, however, is slightly longer than the values reported in the literature.[20,21] The ten-membered ring is very contoured owing to concurrence of the C(1)–C(10) *trans* and C(4)–C(5) *cis* double bonds as well as the C(6)–C(7) *cis*-fused cyclopropane ring in a semi-equatorial configuration. This is reflected in the bond angles: the C–C(sp^3)–C bond angles of the ten-membered ring are in a range 109.6 [110.5] to 124.1° [124.2°], and the mean is 115.1° [115.6°]. The largest deviation from the tetrahedral value is found at the cyclopropane function where the C(5)–C(6)–C(7) is 122.1° [124.2°] and the C(6)–C(7)–C(8) 124.1° [122.6°].

The Dreiding model examination suggested both the molecules of (–)-isobicyclogermacrenal (1) and (–)-lepidozenal (2) have, respectively, the two major conformers (a) and (b), and (c) and (d) (see Figure 3). Any other conformations seem highly improbable on consideration of the steric hindrance. The overall conformation of the present alcohol (7) approximates to the framework corresponding to the conformer (a) which is described as a chair-twist type, having the two substituents in a *syn* orientation on the α-face of the molecule.

This conformation is, on the whole, in agreement with that of the mother hydrocarbon isobicyclogermacrene whose conformation had been determined by n.O.e. experiments,[11] although this is an enantiomeric form of the present (–)-*ent*-isobicyclogermacrene (9). Recently, the n.O.e. measurement and the molecular mechanics calculation had indicated that the more stable conformer of the *trans,cis*-cyclodeca-1,5-dienes is a twist-chair or a twist-twist form in the ground state; the two double-bonds have a parallel orientation and the two alkyl groups an *anti*-arrangement.[22-24] However, when the number of other strained functional groups, *e.g.* cyclopropane, lactone, and epoxy rings, increases, the stability of the ten-

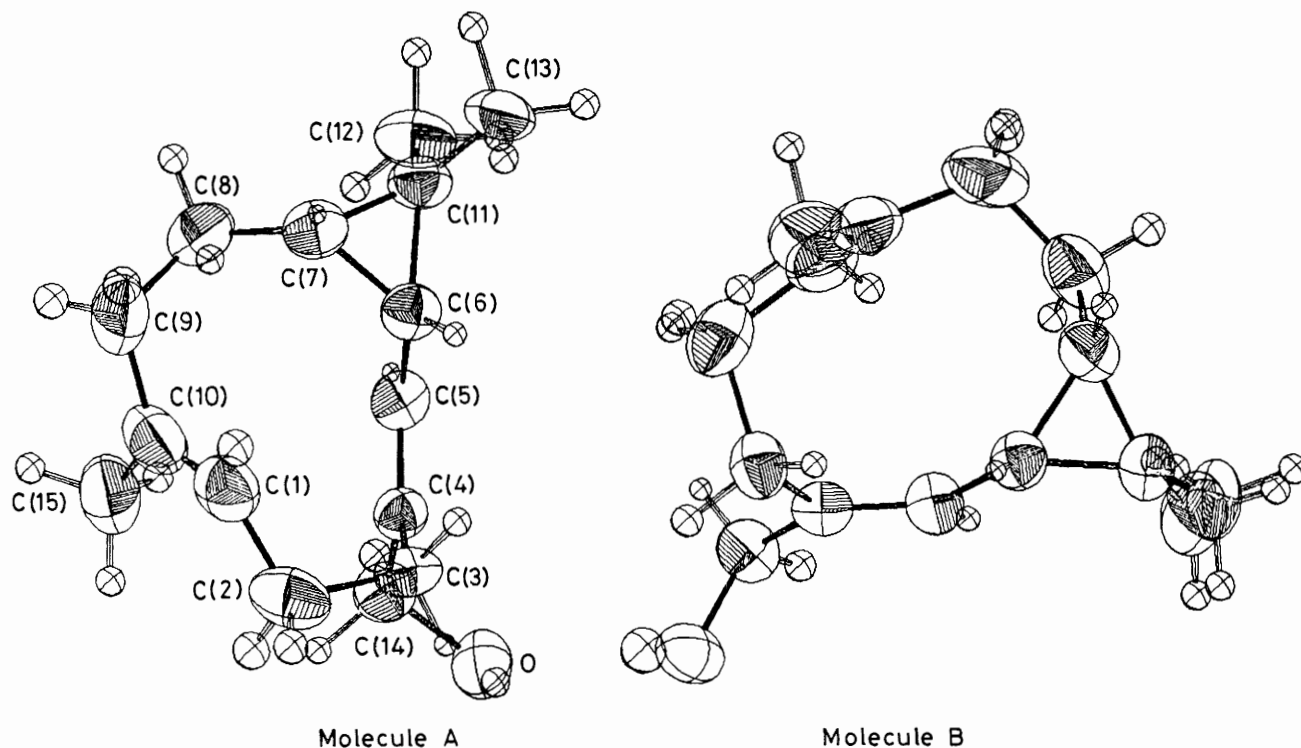Molecule A   Molecule B

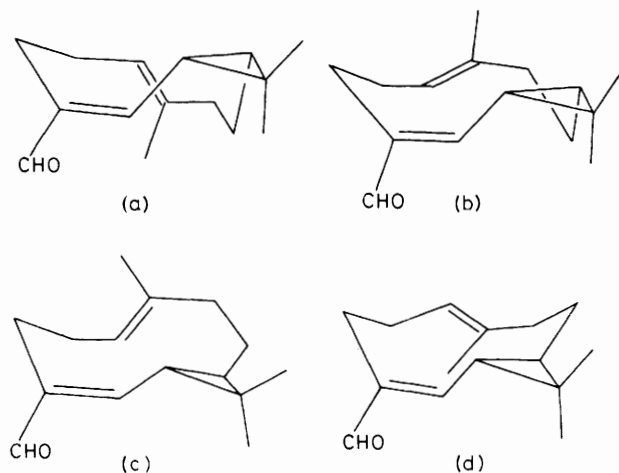**Figure 2.** A perspective drawing of an X-ray model of ($+$)-isobicyclogermacrenol (7)

Figure 3. Possible molecular conformations for ($-$)-isobicyclogermacrenal (1) and ($-$)-lepidozenal (2)

membered ring becomes more complicated.[25] In this ($+$)-isobicyclogermacrenol (7) the carbon framework takes advantage of its flexibility to assume a chair-twist conformation which is, furthermore, characterized by the endocyclic torsion angles (see Table 4).

($-$)-Isobicyclogermacrenal (1) gave a u.v. spectrum showing a broad absorption band at 261 nm (ϵ 11 600). Its reduced products (7) and (9) lost the absorption attributable to the conjugated enal function, and their spectra still exhibited bands at 215 (ϵ 7 880) and at 212 nm (ϵ 8 560), respectively. These absorptions can be interpreted in terms of either the conjugation of the *cis* double bond with the cyclopropane ring or the transannular interaction between the two double bonds.[26,27] In the former, since the angle between the C(3)—

C(4)—C(5)—C(6) plane and the C(6)—C(11)—C(7) one is 71.2° [68.8°], it is difficult to produce the interaction due to a conjugation of the *cis* double bond with the cyclopropane ring; in the latter, the C(1) $\cdots$ C(4) and C(1) $\cdots$ C(5) transannular separations {2.978 [2.982] and 3.248 Å [3.244 Å]} are distinctly short and the torsion angle C(4)—C(5) $\cdots$ C(1)—C(10) is 125° [125°].[28] These results indicate that the relation between the two double bonds in the present chair-twist conformer is similar to that of the crossed orientation which produces a significant π–π interaction encountered in the *trans,cis*-cyclodeca-1,5-diene, *e.g.* pregeijerene[29,30] and eupatolide.[26] Therefore, this characteristic u.v. absorption is considered to be rationalized in terms of the transannular proximity of the two double bonds.

The crystal structure in projection along the a-axis is illustrated in Figure 4. The two independent molecules in the asymmetric unit are linked by intermolecular hydrogen bonding through the hydroxy groups, OA $\cdots$ HOB (1.865 Å); this unit is further linked with others by the same bond around the 2_1 screw axis along the a-direction. Consequently, in the crystal, the hydroxy groups tend to congregate in one region and the aliphatic rings in another. All intermolecular distances are calculated and the most significant contacts (<3.60 Å) are given in Table 5. The molecular packing is efficient with several contacts approaching the sum of the van der Waals radii; the shortest non-hydrogen contact is 2.498 Å.

On the other hand, with the *trans,cis*-cyclodeca-1,5-diene having a *trans*-fused cyclopropane ring, ($-$)-lepidozenal (2), the C(10)-methyl signals of ($-$)-lepidozenal (2) and ($-$)-lepidozenol (13) appeared in the ^{1}H n.m.r. spectra at δ 1.64 and 1.63, respectively, there being no shielding effects from the C(4)—C(5) double bond and/or the C(4)-carbonyl group; this contrasts with the upfield shift of the methyls of ($-$)-isobicyclogermacrenal (1) [δ 1.25] and ($+$)-isobicyclogermacrenol (7) [δ 1.36]. Furthermore, a n.O.e. value between the 10-methyl

Table 3. Bond lengths (Å) and bond angles (°), with estimated standard deviations in parentheses

(a) Distances	Molecule (A)	Molecule (B)
O–C(14)	1.430(7)	1.425(7)
C(1)–C(2)	1.492(10)	1.502(10)
C(1)–C(10)	1.305(10)	1.308(10)
C(2)–C(3)	1.546(8)	1.537(8)
C(3)–C(4)	1.509(7)	1.503(7)
C(4)–C(5)	1.321(7)	1.319(7)
C(4)–C(14)	1.502(7)	1.512(7)
C(5)–C(6)	1.482(7)	1.483(7)
C(6)–C(7)	1.528(7)	1.523(7)
C(6)–C(11)	1.531(7)	1.514(7)
C(7)–C(8)	1.490(9)	1.508(9)
C(7)–C(11)	1.510(8)	1.505(8)
C(8)–C(9)	1.538(11)	1.534(11)
C(9)–C(10)	1.503(11)	1.492(10)
C(10)–C(15)	1.501(11)	1.514(11)
C(11)–C(12)	1.513(8)	1.473(10)
C(11)–C(13)	1.493(8)	1.525(10)

(b) Angles		
C(2)–C(1)–C(10)	127.0(6)	128.4(6)
C(1)–C(2)–C(3)	109.6(5)	110.5(5)
C(2)–C(3)–C(4)	111.9(4)	112.2(4)
C(3)–C(4)–C(5)	123.5(4)	124.9(4)
C(3)–C(4)–C(14)	115.9(4)	115.0(4)
C(5)–C(4)–C(14)	120.4(4)	119.9(4)
C(4)–C(5)–C(6)	126.6(4)	126.0(4)
C(5)–C(6)–C(7)	122.1(4)	124.2(4)
C(5)–C(6)–C(11)	123.2(4)	124.2(4)
C(7)–C(6)–C(11)	59.2(3)	59.4(3)
C(6)–C(7)–C(8)	124.1(5)	122.6(5)
C(6)–C(7)–C(11)	60.5(3)	60.0(3)
C(8)–C(7)–C(11)	126.5(5)	125.6(5)
C(7)–C(8)–C(9)	111.7(5)	112.4(5)
C(8)–C(9)–C(10)	111.0(6)	111.8(6)
C(1)–C(10)–C(9)	121.1(6)	119.5(6)
C(1)–C(10)–C(15)	125.3(6)	123.6(6)
C(9)–C(10)–C(15)	113.3(6)	116.6(6)
C(6)–C(11)–C(7)	60.3(3)	60.6(3)
C(6)–C(11)–C(12)	116.3(4)	117.2(5)
C(6)–C(11)–C(13)	119.4(4)	119.0(5)
C(7)–C(11)–C(12)	117.9(4)	117.2(5)
C(7)–C(11)–C(13)	119.4(4)	117.6(5)
C(12)–C(11)–C(13)	113.6(4)	114.7(5)
O–C(14)–C(4)	110.6(4)	110.5(4)

and the 5-H was not observed, although the n.O.e. in the first, (1), appeared as 12%. Therefore, the stable conformation of (−)-lepidozenal (2) was deduced to be the conformer (c) holding the methyl and the formyl group in an *anti* relationship. This conformation corresponds to that of heliangolides which are constituted of the *trans,cis*-germacradiene having a *trans*-fused butenolide at C(6) and C(7) positions.[31]

It is generally known that *trans*-farnesyl pyrophosphate (23) and the *cis*-isomer (24) generate various monocarbocyclic cations by enzymatic regiospecific cyclizations through the intermediacy of non-classical cations.[32–34] These cations should be neutralized by bonding with nucleophilic groups in the active sites of enzymes. These cations follow the regiospecific and stereoselective cyclization *via* some alkyl migrations and bond cleavages to produce the individual types of sesquiterpene carbon frameworks. Interestingly, it is certain that both enantiomers, (+)-6,11-cyclogermacrene (25) and (−)-*ent*-6,11-cyclogermacrene (4), occurring in higher plants and liverworts respectively, are formed from the delocalized cation (e) generated from *trans*-FPP (23) by stereoselective 1,3-

Table 4. Selected torsion angles (°)

	Molecule (A)	Molecule (B)
C(10)–C(1)–C(2)–C(3)	94.5	95.0
C(2)–C(1)–C(10)–C(15)	9.2	9.8
C(1)–C(2)–C(3)–C(4)	− 61.2	− 60.2
C(2)–C(3)–C(4)–C(5)	87.4	90.9
C(3)–C(4)–C(5)–C(6)	2.3	4.1
C(4)–C(5)–C(6)–C(7)	− 113.4	− 112.8
C(5)–C(6)–C(7)–C(8)	4.0	2.6
C(6)–C(7)–C(8)–C(9)	90.2	89.9
C(7)–C(8)–C(9)–C(10)	− 69.9	− 71.1
C(8)–C(9)–C(10)–C(1)	89.5	90.6
C(9)–C(10)–C(1)–C(2)	− 163.8	− 163.0

Table 5. Intermolecular distances with standard deviations (<3.0 Å)

OA · · · OB[I]	2.707(6)	C(6)B · · · C(8)B[III]	2.659(8)
C(1)B · · · C(4)B[II]	2.982(8)	C(6)B · · · C(13)B[I]	2.618(9)
C(2)B · · · C(10)B[III]	2.531(10)	C(7)B · · · C(12)B[I]	2.543(9)
C(3)B · · · C(5)[II]	2.503(8)	C(7)B · · · C(13)B[II]	2.591(9)
C(3)B · · · C(15)B[II]	2.544(8)	C(8)B · · · C(10)B[V]	2.506(9)
C(4)B · · · C(6)B[III]	2.498(7)	C(8)B · · · C(11)B[II]	2.680(9))
C(5)B · · · C(7)B[IV]	2.656(8)	C(12)B · · · C(13)B[VI]	2.525(12

Roman numerals as superscripts refer to the following equivalent positions relative to the reference molecule at x, y, z:

I	$\frac{1}{2} + x, \frac{1}{2} - y, -z$	IV	$-1 + x, y, z$
II	$1 + x, y, z$	V	$-x, \frac{1}{2} + y, \frac{1}{2} - z$
III	$-\frac{1}{2} + x, \frac{1}{2} - y, -z$	VI	$\frac{3}{2} + x, \frac{1}{2} - y, -z$

deprotonation reactions of the different enzyme systems of the plants (Scheme 4). Alternatively, *cis*-FPP (24) is converted into the delocalized cation (f), and the other one, through the removal of the pyrophosphate anion accompanied by participation of either the terminal or central double bonds, respectively. In a manner analogous to the above example, the key sesquiterpenes (+)-isobicyclogermacrene (9) and (−)-lepidozene (15), or their derivatives, are stereoselectively produced from the cyclized carbocationic intermediate (f) by the 1,3-deprotonation reaction of liverwort enzymes (Scheme 5). Although (−)-lepidozenal (2) holds the 7-alkyl substituent in the β-configuration, the liverwort sesquiterpenoids are usually enantiomeric forms of those of higher plants and should have the α-substituents at the 7-position;[1] such formation of the cyclopropane ring of (−)-lepidozene (15) should directly proceed through the above described intermediate cation (f), but might not be produced in a stepwise fashion from any cations of the germacrane skeleton.[35]

Therefore, the isolation of (−)-isobicyclogermacrenal (1) and (−)-lepidozenal (2) is very important evidence in support both of the direct contribution of hypothetical intermediates, such as the delocalized cations (e) and (f), and the stereoselective deprotonation reaction in the sesquiterpenoid biogenesis as proposed by Ruzicka, Hendrickson, and other workers.[36–38]

Otherwise, besides (−)-aromadendrene (5) and (+)-vitrenal (6) from this liverwort, we have isolated a number of the *ent*-type sesquiterpenoids containing a *cis*-junctioned *gem*-dimethyl cyclopropane ring as the characteristic component of the liverworts,[1c] *e.g.* (+)-maalian-5-ol (26),[39] (−)-maalioxide (27),[40] (+)-cyclocolorenone (28),[40] (−)-hanegokedial (29),[2a] (+)-ovalifoliene (30),[2a] (−)-myliol (31),[41] and (−)-spathulenol (32).[42] These sesquiterpenoids are basically classified into the 6,6,3- and 5,7,3-tricyclic ring systems which are furthermore grouped into the *trans* and *cis* types of the AB
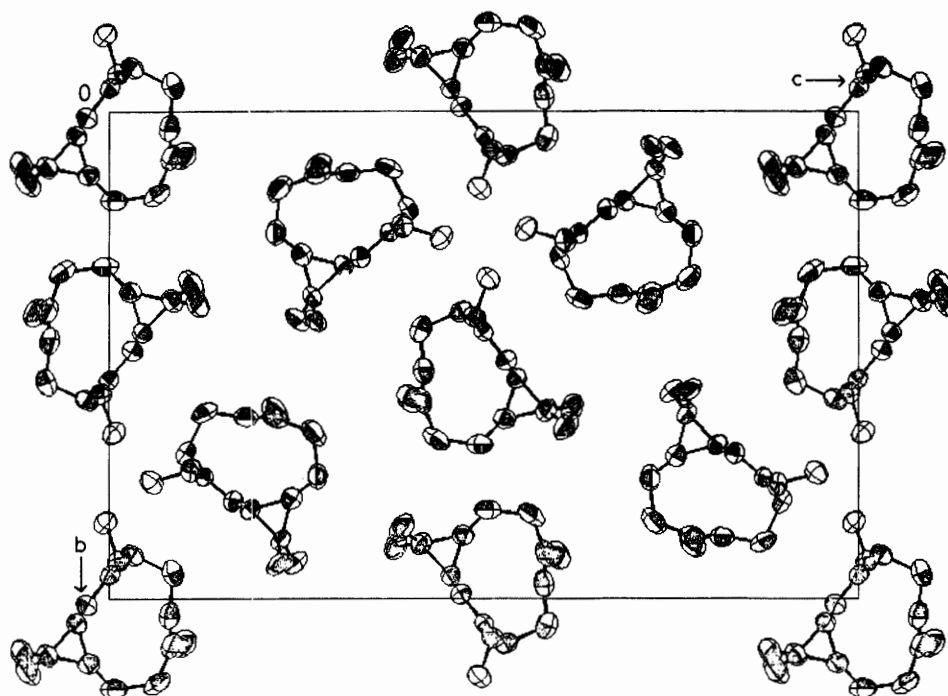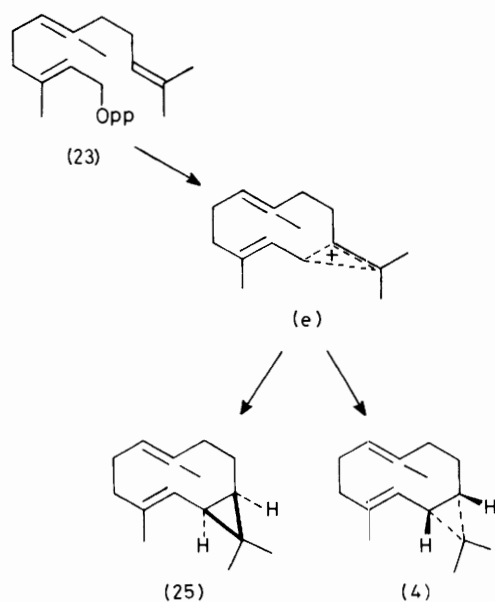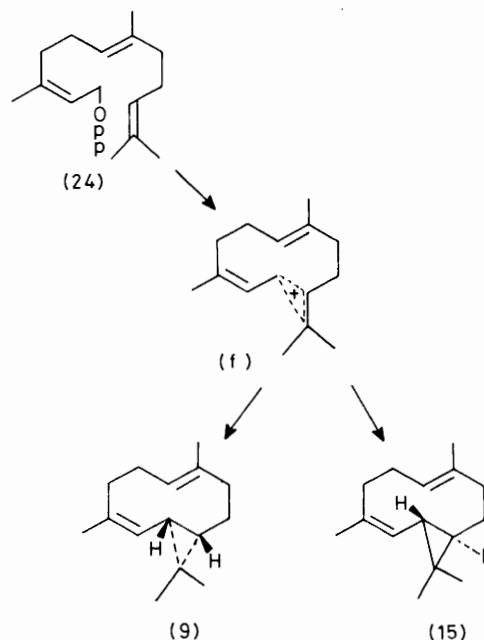
Figure 4. A crystal structure in projection along the *a*-axis of (+)-isobicyclogermacrenol (7)


Scheme 4. Biogenesis of (+)-bicyclogermacrene (25) and (−)-*ent*-bicyclogermacrene (4) from the delocalized cation (e) by the stereoselective 1,3-deprotonation reactions

Scheme 5. Biogenesis of (−)-isobicyclogermacrene (9) and (−)-lepidozene (15) from the delocalized cation (f) by the stereoselective 1,3-deprotonation reactions

ring juncture. When each of the stable conformations (g) and (h) of the two key sesquiterpenes *ent*-bicyclogermacrene (4) and *ent*-isobicyclogermacrene (9) undergoes Markownikoff and anti-Markownikoff type *trans*-antiparallel cyclizations (Scheme 6), two pairs of the carbon frameworks, *ent*-maaliane (i) and *ent*-alloaromadendrane (j), and *ent*-allomaaliane (k) and *ent*-aromadendrane (l), theoretically form, although allomaaliane type (k), named tentatively, is not known in nature.[9] Speculatively, the *ent*-aromadendrane framework (l) also may form from an unstable conformer of *ent*-bicyclogermacrene, but it

must be made from the stable conformer of *ent*-isobicyclogermacrene. However, the possibility of *trans-cis* isomerization of the double bond may not be neglected in the cyclodeca-1,5-diene nucleus. The three carbon frameworks thus formed are then transformed by the subsequent regiospecific and stereoselective cyclizations and alkyl migrations and/or bond cleavages followed by the appropriate oxidations into the above liverwort sesquiterpenoids (5), (6), (26)—(32) specific to the plant species.
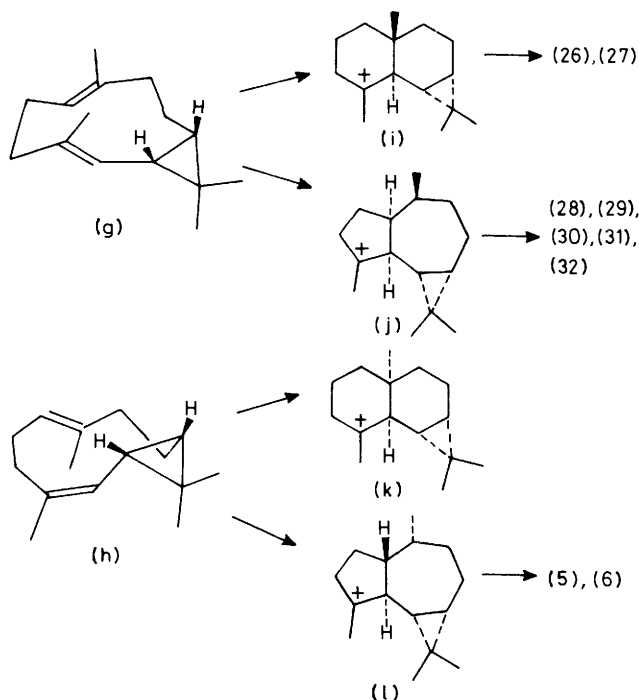
Scheme 6. Formation of the liverwort sesquiterpenoids from the stable conformers of *ent*-bicyclogermacrene (g) and *ent*-isobicyclogermacrene (h) *via* the cyclized intermediate cations (i), (j), and (l)

Biological Activity.—The plant-growth-inhibitory activity of the two novel sesquiterpene aldehydes (−)-isobicyclogermacrenal (1) and (−)-lepidozenal (2), and their hydroxy derivatives, (7) and (13), was tested on rice seedlings. Compounds (1) and (2) inhibit completely the growth of leaves and roots in concentrations of 50 (2.3 × 10⁻⁴) and 250 p.p.m. (1.1 × 10⁻³M), respectively. The former is also a strong growth inhibitor at 6 and 7 p.p.m. showing 50% growth inhibition (I_{50}) with respect to the leaves and roots. Although the hydroxy derivative (7) exhibits reduced activity with respect to (1), the alcohol (13) inhibits at a concentration of 100 p.p.m., an increase of activity with respect to (2). The details of the biological activity will be reported elsewhere.

Experimental

M.p.s are uncorrected. Optical rotations were taken on an automatic polarimeter in chloroform solutions at room temperature (25 °C), and u.v. spectra were measured in ethanol solutions. Unless stated otherwise, i.r. spectra were recorded in tetrachloromethane solutions on a grating spectrometer. ¹H N.m.r. (60, 90, or 100 MHz) and ¹³C n.m.r. (22.63 MHz) spectra were for deuteriochloroform solutions with tetramethylsilane as internal standard. For n.O.e. experiments the spectra were determined in degassed chloroform solutions; the enhancement expressed in % was an average value of five times in integrated intensity. Low- and high-resolution mass spectra were determined at 70 eV (the relative intensities given herein are those of the low-resolution mass spectra). G.l.c. was performed using stainless steel columns (3 mm × 2 m) packed with either 5% DEGS, 5% SE-30, or 5% OV-1 on 80—100 mesh Chromosorb AW at a N₂-flow of 40 ml/min. For column chromatography Merk Kieselgel 60 was used and Merk Kieselgel 60 PF₂₅₄ was used for t.l.c. and p.l.c. Analytical plates were visualized under u.v. light or were sprayed with

20% sulphuric acid in ethanol and then heated at 100 °C for 10 min. All the reaction products in this work were purified by column chromatography and/or p.l.c. using the mixed solvent of hexane and ethyl acetate, and the homogeneity of gummy compounds was established by g.l.c., t.l.c., and ¹H n.m.r. spectroscopy.

Extraction and Isolation.—The liverwort *Lepidozia vitrea* was collected in a forest of Kuju-machi in Oita-prefecture. The whole plants (5.3 kg), after being dried in the shade for several days, were digested with methanol. The methanol extract (180 g) obtained by removal of the solvent under reduced pressure was again extracted with ether. The ethereal solution was evaporated under reduced pressure to give a brown viscous substance (87.0 g). The extract (85.0 g) was chromatographed through a silica gel column with hexane–ethyl acetate (7 : 1). Each portion was then subjected to a further combination of column chromatography and p.l.c. using silica gel to isolate the two sesquiterpene aldehydes, (−)-isobicyclogermacrenal (1) (775 mg) and (−)-lepidozenal (2) (940 mg), together with three enantiomeric type sesquiterpene hydrocarbons, (−)-β-pompene (3), (−)-*ent*-bicyclogermacrene (4), and (−)-*ent*-aromadendrene (5), and the third sesquiterpene aldehyde (+)-vitrenal (6). The physical properties of the two aldehydes are listed below.

(−)-*Isobicyclogermacrenal* [(6R,7S)-6,11-*cyclogermacra*-1(10)E,4E-*dien*-14-*al*] (1): [α]$_D$ − 168° (*c*, 1.00) (Found: M⁺, 218.1659. C₁₅H₂₂O requires M, 218.1668); λ$_{max.}$ 261 nm (ε 11 600); ν$_{max.}$ 3 040, 2 810, 2 705, 1 685, 1 625, 1 417, 1 382, 1 377, 1 250, 1 188, 1 143, 1 070, and 863 cm⁻¹; δ$_H$ 0.7—1.1 (2 H, m), 1.18 and 1.21 (each 3 H, s), 1.25 (3 H, d, *J* 1.5 Hz), 5.06 (1 H, br t, *J* 7.0 Hz), 6.28 (1 H, d, *J* 9.0 Hz), and 9.25 (1 H, s); *m/z* 218.1659 (M⁺, C₁₅H₂₂O requires M, 218.1668, 68%), 203.1403 (C₁₄H₁₉O requires 203.1434, 14), 189.1577 (C₁₄H₂₁ requires 189.1642, 19), 175.1089 (C₁₂H₁₅O requires 175.1122, 100), 162.1038 (C₁₁H₁₄O requires 162.1043, 23), 149.0964 (C₁₀H₁₂O requires 148.0887, 13), 133.0655 (C₉H₉O requires 133.0653, 33), 121.0584 (C₈H₉O requires 121.0652, 21), 105.0740 (C₈H₉ requires 105.0703, 48), 91 (66), 79 (48), 67 (37), 55 (42), and 41 (87).

(−)-*Lepidozenal* [(6R,7R)-*lepidoza*-1(10)E,4E-*dien*-14-*al*] (2): [α]$_D$ − 169° (*c*, 1.11) (Found: M⁺, 218.1672. C₁₅H₂₂O requires M, 218.1670); λ$_{max.}$ 265 nm (ε 14 000); ν$_{max.}$ 3 040, 2 820, 2 710, 1 685, 1 630, 1 435, 1 375, 1 369, 1 252, 1 190, 1 136, 1 115, and 870 cm⁻¹; δ$_H$ 0.4—1.3 (2 H, m), 1.15 and 1.25 (each 3 H, s), 1.64 (3 H, d, *J* 1.5 Hz), 5.05 (1 H, br t, *J* 7.0 Hz), 6.33 (1 H, d, *J* 10.0 Hz), and 9.30 (1 H, s); *m/z* 218.1672 (M⁺, C₁₅H₂₂O requires M, 218.1670, 57%), 203.1442 (C₁₄H₁₉O requires 203.1435, 6), 189.1608 (C₁₄H₂₁ requires 189.1641, 17), 175.1155 (C₁₂H₁₅O requires 175.1122, 43), 162.1053 (C₁₁H₁₄O requires 162.1044, 9), 148 (26), 145.1005 (C₁₁H₁₃ requires 145.1016, 7), 135.0857 (C₉H₁₁O requires 135.0810, 22), 133 (57), 119 (27), 117.0699 (C₉H₉ requires 117.0703, 9), 105.0691 (C₈H₉ requires 105.0703, 70), 91 (79), 79 (55), 69 (53), 55 (61), and 41 (100).

Lithium Aluminium Hydride Reduction of (−)-Isobicyclogermacrenal (1).—(−)-Isobicyclogermacrenal (1) (510 mg) in dry ether (5 ml) was added dropwise to a solution of lithium aluminium hydride (95 mg) in dry ether (5 ml), and the mixture was stirred at 0 °C for 30 min and then at room temperature for 30 min. The excess of hydride was decomposed by addition of ice–water (0.2 ml) and 10% sodium hydroxide (0.2 ml) and the white precipitates formed were filtered off. Work-up gave (+)-*isobicyclogermacrenol* [(6R,7S)-6,11-*cyclogermacra*-1(10)E,4E-*dien*-14-*ol*] (7) as crystals (395 mg): m.p. 87—88 °C (from hexane–ethyl acetate, 3 : 1); [α]$_D$ + 21.1° (*c*, 1.09) (Found: C, 81.8; H, 11.2. C₁₅H₂₄O requires C, 81.76; H, 10.98%); λ$_{max.}$

215 nm (ε 7 880); $v_{max.}$ 3 620, 3 385, 1 670, 1 650, 1 217, 1 076, 990, and 860 cm^{-1}; δ_H 0.4—0.9 (2 H, m), 1.03 and 1.07 (each 3 H, s), 1.36 (3 H, d, J 1.5 Hz), 3.99 (2 H, br s), 4.9—5.3 (1 H, br exchangeable with D$_2$O), and 5.22 (1 H, d, J 8.0 Hz); δ_C 15.6 (q), 17.1 (q), 17.7 (s), 23.3 (t), 27.6 (t), 27.6 (t), 27.6 (q), 29.2 (d), 33.6 (d), 40.6 (t), 67.3 (t), 123.7 (d), 126.0 (d), 134.4 (s), and 139.0 (s); m/z 222.1790 (M^+, C$_{15}$H$_{24}$O requires M, 220.1826, 12%), 205.1753 (C$_{14}$H$_{21}$O requires 205.1591, 2), 202.1753 (C$_{15}$H$_{22}$ requires 202.1720, 2), 189.1655 (C$_{14}$H$_{21}$ requires 189.1642, 6), 177.1240 (C$_{12}$H$_{17}$O requires 177.1277, 8), 159.1170 (C$_{12}$H$_{15}$ requires 159.1172, 6), 147.1142 (C$_{11}$H$_{15}$ requires 147.1172, 6), 133.1013 (C$_{10}$H$_{13}$ requires 133.1016, 7), 119.0861 (C$_9$H$_{11}$ requires 119.0860, 12), 105.0699 (C$_8$H$_9$ requires 105.0703, 20), 91 (31), 83 (84), 67 (29), 55 (30), 47 (100), and 43 (21).

Oxidation of (−)-*Isobicyclogermacrenol* (7) *with Manganese Dioxide.*—To a suspension of manganese dioxide (70 mg) in dry ether (3 ml) was added a solution of the alcohol (7) (18 mg) in dry ether with stirring; the mixture was then stirred at room temperature for 24 h. After this it was filtered through a silica gel column and the solvent evaporated under reduced pressure. Work-up afforded the aldehyde (1) as a gum (12 mg); its spectral data and optical rotation were identical with those of the natural aldehyde (1).

Epoxidation of (+)-*Isobicyclogermacrenol* (7).—To a solution of the alcohol (7) (34 mg) in dichloromethane (2 ml) *m*-chloroperbenzoic acid (31 mg) in dichloromethane (1 ml) was added at −10 °C; the mixture was then stirred at −10 °C for 1 h. In the usual way, (+)-*epoxyisobicyclogermacrenol* [(1R,-6R,7S,10S)-1,10-*epoxy*-6,11-*cyclogermacr*-4E-*en*-14-*ol*] was obtained as crystals (22 mg) (8): m.p. 108—109 °C (from hexane–ethyl acetate, 3 : 1); [α]$_D$ +11.9° (c, 0.8) (Found: C, 76.0; H, 10.45. C$_{15}$H$_{24}$O$_2$ requires C, 76.22; H, 10.24%); $v_{max.}$ 3 550, 3 525, 3 450, 1 460, 1 456, 1 380, 1 370, 1 135, 1 080, 1 022, and 875 cm^{-1}; δ_H 1.10 (9 H, s), 3.04 (1 H, dd, J 10.5 and 2.5 Hz), 4.05 (2 H, br s), and 5.41 (1 H, d, J 8.0 Hz); m/z 236 (M^+, 8%), 221 (4), 218 (5), 205 (6), 203 (5), 175 (18), 147 (14), 135 (23), 121 (24), 107 (44), 93 (51), 79 (49), 69 (50), 55 (58), 43 (99), and 41 (100).

Pyridine–Sulphur Trioxide–Lithium Aluminium Hydride Reduction of (+)-*Isobicyclogermacrenol* (7).[12]—Pyridine–sulphur trioxide complex (133 mg) was added to the alcohol (7) (88 mg) in dry ether (10 ml) at −25 °C, and the mixture was stirred at 0 °C for 18 h under nitrogen. Lithium aluminium hydride (120 mg) was then added at −25 °C and the mixture stirred at 0 °C for 1 h and then at room temperature for 4 h. To the reaction mixture water (0.3 ml) and 10% aqueous sodium hydroxide (0.2 ml) were added at 0 °C to decompose the excess of hydride. Work-up gave crude products which were separated by column chromatography into (+)-isobi-cyclogermacrene (9) (23 mg) and an isomer (10) (11 mg).

(+)-*Isobicyclogermacrene* [(6R,7S)-6,11-*cyclogermacra*-1(10)E,4E-*diene*] (9): [α]$_D$ +14.8° (c, 1.02); $\lambda_{max.}$ 212 nm (ε 8 560); $v_{max.}$ 3 080, 1 670, 1 650, 1 418, 1 130, 1 084, 990, 875, and 845 cm^{-1}; δ_H 0.3—1.0 (2 H, m), 1.00 and 1.06 (each 3 H, s), 1.42 and 1,72 (each 3 H, d, J 1.5 Hz), 4.96 (1 H, d, J 8.5 Hz), and 4.7—5.15 (1 H, m); δ_C 15.8 (q), 17.0 (q), 17.1 (s), 23.3 (t), 24.5 (q), 27.0 (t), 27.8 (d), 29.2 (q), 32.0 (t), 33.0 (d), 40.8 (t), 123.6 (d), 123.9 (d), 134.7 (s), and 135.4 (s); m/z 204 (M^+, 52%), 189 (14), 161 (48), 147 (21), 133 (27), 121 (100), 105 (54), 93 (79), 79 (47), 67 (28), 55 (41), and 41 (83).

(+)-β-*Isobicyclogermacrene* [(6R,7S)-6,11-*cyclogermacra*-1(10)E,4(14)-*diene* (10): [α]$_D$ +4.0° (c, 1.01); $v_{max.}$ 3 060, 1 635, 1 222, 1 195, 1 142, 987, 892, 878, and 837 cm^{-1}; δ_H 0.1—0.7 (2 H, m), 0.78 and 1.04 (each 3 H, s), 1.66 (3 H, d,

J 1.5 Hz), 4.83 (2 H, br s), and 5.28 (1 H, br t, J 7.0 Hz); m/z 204 (M^+, 25%), 189 (11), 161 (53), 149 (23), 133 (26), 119 (29), 105 (46), 93 (59), 82 (100), 67 (46), 55 (44), and 41 (96).

Ozonolysis of (+)-*Isobicyclogermacrenol* (7).—To a solution of the alcohol (7) (140 mg) in ethyl acetate (15 ml) ozonized oxygen gas was passed at −80 °C for 2 h. The solvent was evaporated under reduced pressure and the residue heated with water (10 ml) and 35% hydrogen peroxide (0.1 ml) at 50—60 °C for 2 h. From the reaction mixture (1R,3S)-2,2-dimethyl-3-(3-oxobutyl)cyclopropanecarboxylic acid (11) was isolated as a gum (44 mg): [α]$_D$ −17.9° (c, 1.16) [lit.,[1b] [α]$_D$ −20.6°]; $v_{max.}$ 3 500—2 500, 1 725, 1 695, 1 415, 1 233, 1 166, 1 138, and 1 098 cm^{-1}; δ_H 1.18 and 1.24 (each 3 H, s), 1.46 (1 H, d, J 8.0 Hz), 2.16 (3 H, s), and 10.20 (1 H, br, exchangeable with D$_2$O); m/z 166 ([M − 18]$^+$, 2%), 151 (2), 141 (3), 126 (19), 113 (7), 95 (14), 83 (19), 67 (13), 55 (12), and 43 (100).

Methylation of the cis-*Keto Acid* (11) *with Diazomethane.*—An ethereal solution of diazomethane was added to a solution of the acid (11) (23 mg) in ether (3 ml); on work-up (1R,3S)-methyl2,2-dimethyl-3-(3-oxobutyl)cyclopropanecarboxylate(12) was isolated as a gum (22 mg): [α]$_D$ −22.6° (c, 0.65) (lit.,[1b] [α]$_D$ −25.1°); $v_{max.}$ 1 730, 1 422, 1 195, 1 175, 1 160, 1 135, and 1 095 cm^{-1}; δ_H 1.16 and 1.23 (each 3 H, s), 1.45 (1 H, d, J 8.0 Hz), 2.14 (3 H, s), and 3.64 (3 H, s); δ_C 14.3 (q), 18.2 (t), 25.7 (s), 28.4 (d), 29.0 (q), 29.8 (q), 33.0 (d), 43.5 (t), 51.1 (q), 172.2 (s), and 208.6 (s); m/z 183 ([M − 15]$^+$, 2%), 167 (3), 166 (4), 140 (20), 127 (13), 116 (9), 109 (8), 95 (23), 81 (15), 67 (18), 55 (12), and 43 (100).

Reduction of (−)-*Lepidozenal* (2) *with Lithium Aluminium Hydride.*—The aldehyde (2) (380 mg) in dry ether (5 ml) was added to a suspension of lithium aluminium hydride (69 mg) in dry ether (6 ml). The mixture was stirred at 0 °C for 30 min and then at room temperature for 30 min. The reaction product was treated by the same procedure as in the case of the aldehyde (1), and (−)-lepidozenol [(6R,7S)-*lepidoza*-1(10)E,4E-*dien*-14-*ol*] (13) was obtained as a gum (275 mg): [α]$_D$ −104° (c, 1.75) (Found: M^+, 220.1794. C$_{15}$H$_{24}$O requires M, 220.1825); $\lambda_{max.}$ 211 nm (ε 6 700); $v_{max.}$ 3 610, 3 350, 1 670, 1 650, 1 100, 975, 962, 905, and 865 cm^{-1}; δ_H 0.05—1.0 (2 H, m), 1.03 and 1.12 (each 3 H, s), 1.63 (3 H, d, J 1.5 Hz), 4.05 (2 H, br s), 5.0—5.4 (1 H, m), and 5.28 (1 H, d, J 9.5 Hz); δ_C 15.5 (q), 19.5 (s), 21.8 (q), 22.4 (q), 24.6 (t), 26.9 (t), 27.1 (t), 31.8 (d), 34.3 (d), 40.4 (t), 67.9 (t), 126.1 (d), 128.3 (d), 133.1 (s), and 136.8 (s); m/z 220.1794 (M^+, C$_{15}$H$_{24}$O requires 220.1825, 7%), 202.1705 (C$_{15}$H$_{22}$ requires 202.1719, 5), 189.1655 (C$_{14}$H$_{21}$ requires 189.1642, 6), 177.1313 (C$_{12}$H$_{17}$O requires 177.1279, 6), 159.1152 (C$_{12}$H$_{15}$ requires 159.1172, 12), 145.0999 (C$_{11}$H$_{13}$ requires 145.1016, 11), 131.0856 (C$_{10}$H$_{11}$ requires 131.0859, 19), 119.0855 (C$_9$H$_{11}$ requires 119.0859, 23), 105.0699 (C$_6$H$_9$ requires 105.0703, 46), 91 (100), 79 (77), 67 (74), 53 (69), and 43 (34).

Oxidation of (−)-*Lepidozenal* (13) *with Manganese Dioxide.*—The alcohol (13) (72 mg) was oxidized with manganese dioxide (145 mg) in dry ether (5 ml) by a method similar to that described above to give the original aldehyde (2) as a gum (23 mg). The spectral properties and the optical rotation were identical with those of the natural product (−)-lepidozenal (2).

Epoxidation of (−)-*Lepidozenal* (2).—*m*-Chloroperbenzoic acid (53 mg) in dichloromethane (2 ml) was added to a solution of the aldehyde (2) (61 mg) in dichloromethane (3 ml) and the mixture was stirred at 0 °C for 1 h. Work-up gave (−)-epoxylepidozenal [(1R,6R,7R,10R)-1,10-*epoxylepidoz*-4E-*en*-14-*al*] (14) as a gum (46 mg): [α]$_D$ −133.7° (c, 0.8); $v_{max.}$ 2 720, 1 685, 1 632, 1 385, 1 380, 1 371, 1 155, 1 130, 1 090, 908, 878,

and 870 cm⁻¹; δ_H 1.22, 1.25, and 1.36 (each 3 H, s), 6.41 (1 H, d, J 10.0 Hz), and 9.33 (1 H, s); m/z 234 (M^+, 18%), 219 (11), 205 (11), 191 (14), 163 (21), 149 (22), 135 (20), 121 (23), 107 (39), 93 (40), 83 (59), 69 (38), 55 (45), and 43 (100).

Formation of (−)-*Lepidozene* (15) *and its Isomer* (16) *from the* (−)-*Lepidozenol* (13) *by Pyridine–Sulphur Trioxide–Lithium Aluminium Hydride Reduction.*[12]—Reduction of the alcohol (13) (132 mg) using pyridine–sulphur trioxide complex (200 mg) and lithium aluminium hydride (180 mg) as described above produced (−)-lepidozene (15) (57 mg) and the isomer (16) (11 mg).

(−)-*Lepidozene* [(6R,7R)-*lepidoza*-1(10)E,4E-*diene*] (15): $[\alpha]_D$ −104° (c, 1.16); $\lambda_{max.}$ 214 nm (ε 7 800); $\nu_{max.}$ 1 665, 1 144, 1 126, 1 097, 970, 870, and 830 cm⁻¹; δ_H −0.1—1.1 (2 H, m), 1.01 and 1.09 (each 3 H, s), 1.63 and 1.76 (each 3 H, d, J 1.5 Hz), 4.99 (1 H, d, J 9.0 Hz), and 5.18 (1 H, t, J 8.0 Hz); δ_C 15.5 (q), 19.0 (s), 21.9 (q), 22.4 (q), 24.1 (q), 25.0 (t), 26.1 (t), 31.3 (t), 32.1 (d), 34.1 (d), 40.5 (t), 125.5 (d), 126.3 (d), 132.9 (s), and 133.4 (s); m/z 204 (M^+, 49%), 189 (21), 175 (4), 161 (53), 147 (21), 133 (30), 119 (89), 105 (62), 93 (89), 79 (55), 67 (41), 55 (48), and 41 (100).

(−)-β-*Lepidozene* [(6R,7R)-*lepidoza*-1(10)E,4(14)-*diene*] (16): $[\alpha]_D$ −3.6° (c, 0.54); $\nu_{max.}$ 3 070, 1 675, 1 640, 1 198, 1 130, 1 108, 1 075, 980, and 885 cm⁻¹; δ_H 0.98 (6 H, s), 1.54 (3 H, d, J 1.5 Hz), 4.83 (2 H, br s), and 5.0—5.5 (1 H, m); m/z 204 (M^+, 5%), 189 (3), 175 (1), 161 (13), 149 (8), 153 (11), 119 (14), 105 (24), 93 (43), 82 (100), 67 (33), 55 (33), and 41 (61).

Ozonolysis of (−)-*Lepidozenol* (13) *and Methylation of the* trans-*Keto Acid* (17).—The alcohol (13) (235 mg) in ethyl acetate (25 ml) was ozonolysed by a method similar to that used for the alcohol (7), to give the *trans*-keto acid (17) as a gum (52 mg). The acid (17) (46 mg) was methylated with diazomethane to produce the *trans*-keto ester (18) as a gum (40 mg).

(1R,3R)-2,2-*Dimethyl*-3-(3-*oxobutyl*)*cyclopropanecarboxylic acid* (17): $[\alpha]_D$ −7.2° (c, 0.96); $\nu_{max.}$ 3 500—2 500, 1 715, 1 695, 1 300, 1 170, 1 122, and 963 cm⁻¹; δ_H 1.20 and 1.27 (each 3 H, s), 2.17 (3 H, s), and 10.48 (1 H, br, exchangeable with D₂O); m/z 166 ([M − 18]⁺, 1%), 138 (2), 126 (11), 113 (4), 95 (10), 83 (11), 67 (11), 55 (12), and 43 (100).

(1R,3R)-*Methyl* 2,2-*dimethyl*-3-(3-*oxobutyl*)*cyclopropanecarboxylate* (18): $[\alpha]_D$ −17.8° (c, 0.70); $\nu_{max.}$ 1 730, 1 290, 1 245, 1 195, 1 175, 1 160, 1 120, and 1 050 cm⁻¹; δ_H 1.18 and 1.22 (each 3 H, s), 2.16 (3 H, s), and 3.67 (3 H, s); δ_C 20.9 (q), 21.1 (q), 22.7 (t), 27.7 (s), 30.0 (q), 32.9 (d), 32.9 (d), 43.3 (t), 51.3 (q), 173.1 (s), and 208.0 (s); m/z 198 (M^+, 1%), 183 (3), 166 (8), 151 (3), 140 (46), 127 (30), 116 (17), 109 (16), 95 (51), 81 (27), 67 (23), 55 (14), and 43 (100).

Methanolysis of (+)-β-*Allethrin.*—To a solution of (+)-β-allethrin (2.0 g) in methanol (50 ml) was added toluene-*p*-sulphonic acid (630 mg), and it was refluxed at 85 °C for 24 h. The reaction mixture was evaporated under reduced pressure to half volume and then diluted with water and extracted with ether. Work-up gave (+)-*methyl* trans-*chrysanthemate* [(1R,3R)-*methyl* 2,2-*dimethyl*-3-(2-*methylbut*-1-*enyl*)*cyclopropanecarboxylate*] (19) as a gum (830 mg); $[\alpha]_D$ +24.1° (c, 1.91) (lit.,[43] $[\alpha]_D$ +14.1°); $\nu_{max.}$ 1 725, 1 415, 1 236, 1 206, 1 175, 1 125, and 860 cm⁻¹; δ_H 1.15 and 1.28 (each 3 H, s), 1.37 (1 H, d, J 5.5 Hz), 1.73 (6 H, s), 3.68 (3 H, s), and 4.87 (1 H, br d, J 8.0 Hz); δ_C 18.5 (q), 20.5 (q), 22.2 (q), 25.5 (q), 28.5 (s), 32.8 (d), 34.7 (d), 51.4 (q), 121.3 (d), 135.5 (s), and 170.3 (s); m/z 182 (M^+, 22%), 167 (9), 151 (7), 139 (9), 123 (100), 107 (26), 91 (12), 81 (45), 69 (17), 55 (17), and 41 (35).

Ozonolysis of (+)-*Methyl* trans-*Chrysanthemate* (19).—A solution of the ester (19) (400 mg) in acetic acid (10 ml) was ozonolysed at 0 °C. Ether (10 ml) and zinc dust (700 mg) were added with stirring at 5—15 °C to the solution and then the mixture was stirred at room temperature for 1 h. Work-up gave (1R,3R)-*methyl* 3-*formyl*-2,2-*dimethylcyclopropanecarboxylate* (20) as a gum (138 mg): $[\alpha]_D$ +15.6° (c, 2.18); $\nu_{max.}$ 2 735, 1 730, 1 710, 1 346, 1 280, 1 240, 1 183, 1 125, and 975 cm⁻¹; δ_H 1.32 and 1.35 (each 3 H, s), 2.43 (1 H), 3.69 (3 H, s), and 9.56 (1 H).

Wittig Reaction of the Cyclopropyl Aldehyde (20).—To a solution of 2-oxopropylidenetriphenylphosphorane (133 mg) in methanol (3 ml) the aldehyde (20) (59 mg) was added and the mixture was stirred at room temperature for 2 d. After evaporation of the solvent under reduced pressure, light petroleum was added to the mixture. The crystals of triphenylphosphine oxide formed were filtered off and the filtrate was worked up. Column chromatography of the reaction mixture gave two products as gums: the enone (21) (62 mg) and the double bond isomer (22) (9 mg).

(1R,3R)-*Methyl* 2,2-*dimethyl*-3-(3-*oxobut*-1E-*enyl*)*cyclopropanecarboxylate* (21): $[\alpha]_D$ +125° (c, 1.03); $\nu_{max.}$ 1 730, 1 675, 1 615, 1 205, 1 162, 1 122, 980, and 920 cm⁻¹; δ_H 1.27 and 1.32 (each 3 H, s), 1.81 (1 H, d, J 5.5 Hz), 2.23 (3 H, s), 3.70 (3 H, s), 6.20 (1 H, d, J 15.5 Hz), and 6.55 (1 H, dd, J 15.5 and 7.5 Hz); m/z 196 (M^+, 3%), 181 (2), 164 (7), 153 (10), 137 (17), 122 (17), 95 (33), 82 (23), 55 (6) and 43 (100).

(1R,3R)-*Methyl* 2,2-*dimethyl*-3-(3-*oxobut*-1Z-*enyl*)*cyclopropanecarboxylate* (22): $[\alpha]_D$ +75.1° (c, 0.59); $\nu_{max.}$ 1 730, 1 690, 1 600, 1 215, 1 165, 1 115, and 970 cm⁻¹; δ_H 1.18 and 1.34 (each 3 H, s), 1.67 (1 H, d, J 5.5 Hz), 2.23 (3 H, s), 3.26 (1 H, dd, J 9.5 and 5.5 Hz), 3.68 (3 H, s), 5.68 (1 H, dd, J 11.5 and 9.5 Hz), and 6.23 (1 H, d, J 11.5 Hz); m/z 196 (M^+, 2%), 181 (3), 164 (5), 153 (6), 137 (14), 122 (17), 95 (36), 82 (100), 55 (9), and 43 (86).

Catalytic Hydrogenation of the Enone (21).—The enone (21) (61 mg) was hydrogenated over Adams catalyst (7 mg) in methanol (5 ml) at room temperature for 1 h. Work-up gave (1R,3R)-*methyl* 2,2-*dimethyl*-3-(3-*oxobutyl*)*cyclopropanecarboxylate* (18) as a gum (58 mg): $[\alpha]_D$ −29.5° (c, 1.0); $\nu_{max.}$ 1 720, 1 352, 1 280, 1 236, 1 195, 1 160, 1 120, and 1 050 cm⁻¹; δ_H 1.17 and 1.21 (each 3 H, s), 2.15 (3 H, s), and 3.66 (3 H, s); m/z 198 (M^+, 2%), 183 (1), 167.1099 ([M − 31]⁺, $C_{10}H_{15}O_2$ requires 167.1071, 12), 151.0767 ($C_9H_{11}O_2$ requires 151.0758 2), 140.0835 ($C_8H_{12}O_2$ requires 140.0836, 49), 127.0752 ($C_7H_{11}O_2$ requires 127.0758, 21), 109.0657 (C_7H_9O requires 109.0653, 11), 95 (35), 81 (17), 67 (13), 55 (8), and 43 (100).

Hydrolysis of the trans-*Keto Ester* (18).—The *trans*-keto ester (18) (47 mg) was refluxed in a solution of 3.5% ethanolic potassium hydroxide (2 ml) for 8 h. Work-up gave (1R,3R)-2,2-*dimethyl*-3-(3-*oxobutyl*)*cyclopropanecarboxylic acid* (17) as a gum (28 mg); $[\alpha]_D$ −21.9° (c, 1.21); $\nu_{max.}$ 3 500—2 500, 1 710, 1 690, 1 287, 1 170, 1 120, and 960 cm⁻¹; δ_H 1.19 and 1.26 (each 3 H, s), 2.15 (3 H, s), and 9.63 (1 H, br, exchangeable with D₂O).

Crystal Data.—(+)-*Isobicyclogermacrenol* (7), $C_{15}H_{24}O$, M = 220.4, Orthorhombic, a = 6.457(1), b = 16.919(3), c = 25.936(6) Å, U = 2 833.3 Å³, Z = 8, D_c = 1.03 g cm⁻³, $F(000)$ = 976, $\lambda(\text{Mo-}K_\alpha)$ = 0.7107 Å, $\mu(\text{Mo-}K_\alpha)$ = 0.7 cm⁻¹, Space group $P2_12_12_1$, from systematic absences.

Crystallographic Measurement.—Preliminary oscillation, Weissenberg, and precession photographs indicated the orthorhombic symmetry and the initial unit-cell parameters. The

accurate unit-cell parameters were obtained by the least-squares procedure applied to the 2θ values of 15 general reflections measured on a Syntex R3 four-circle diffractometer with graphite-monochromated Mo-K_α radiation. All the unique diffraction intensities with $2\theta < 55.0°$ were collected in a variable speed ω-scan mode. The small variation in intensity of the three standard reflections indicated a good crystal stability. The intensities of 2 770 independent reflections were obtained, of which 1 911 having $I > 3\sigma(I)$ were considered to be observed after correction for the Lorentz, polarization, and background effects. No correction was applied for the absorption ($0.2 \times 0.3 \times 0.5$ mm).

Structure Analysis and Refinement.—The structure amplitudes were put on an absolute scale by the method of Wilson (B 4.62 Å^2) and the normalized structure amplitudes $|E|$ were then obtained by using the overall temperature parameters. The structure was solved by the direct non-centrosymmetric phase-determining methods by the use of Multan [44] with a total of 232 reflections having $|E| \geqslant 1.60$, from which a starting set of reflections was selected by the program. An E-map computed from the set of phases having the lowest residual and highest figure-of-merit yielded the positions for all 32 non-hydrogen atoms in an asymmetric unit. A structure-factor calculation gave R 0.19 and this was reduced to 0.14 following three cycles of the block-diagonal least-squares refinement of the positional and isotropic thermal parameters. The subsequent anisotropic refinements were by the full-matrix least-squares methods, the convergence being reached at R 0.12 after three cycles. At this stage a three-dimensional difference synthesis revealed all positions of the 48 hydrogen atoms. The further full-matrix refinements with the non-fixed parameters for 36 hydrogen atoms and with the fixed ones for 12 methyl hydrogen atoms (B_{iso} 5.0 Å^2 for all hydrogens) converged to 0.079 for 1 911 reflections. A final difference synthesis was essentially featureless. The unit weighting schemes were retained throughout the least-squares calculation and the used scattering factors were taken from the published table.[45] The observed and calculated structure factors and the anisotropic thermal parameters are deposited in Supplementary Publication No. 23773 (18 pages).*

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* For details of the Supplementary Publications scheme, see Instructions for Authors (1984), *J. Chem. Soc., Perkin Trans. 1*, 1984, Issue 1.

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