Structures of *ent*-Herbertane Sesquiterpenoids displaying Antifungal Properties from the Liverwort *Herberta adunca*

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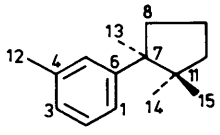
Several aromatic sesquiterpenoids displaying antifungal properties have been isolated from the liverwort *Herberta adunca* together with a mother hydrocarbon with a novel irregular sesquiterpene skeleton, *ent*-herbertane, and their structures and absolute configurations have been determined on the basis of extensive degradation reactions and spectroscopic evidence. The biological activity is also described.

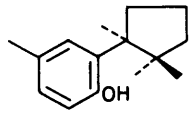
In continuing our studies on the terpenoid constituents of the unique plant group 'liverworts' which contain several oil bodies, characteristic to the species, in each cell of the gametophytes, we have isolated a large variety of sesquiterpenoids in order to ascertain their structures including the absolute configurations. We have found one of the most important biochemical features in biogenesis of the liverwort sesquiterpenoids to be that 'the unique plants, liverworts, elaborate generally the enantiomeric (abbreviated *ent*)-type sesquiterpenoids,' corresponding to the antipodal structures of those of higher plants.[1-3] We have further reported that some of the *ent*-type sesquiterpenoids from liverworts display plant-growth-inhibitory properties.[4-7]

During a search for the biologically active constituents of the liverworts, we examined the antifungal activity of a methanolic extract of the leafy liverwort *Herberta adunca* (Dicks.) S. Gray belonging to the family Herbertaceae of the order Jungermanniales. The liverwort extract depressed the growth of certain plant pathogenic fungi to a remarkable degree in biological tests (50% growth inhibition at 100 p.p.m.). By a combination of column chromatography and preparative layer chromatography (p.l.c.) over silica gel some biologically active sesquiterpene phenols were isolated, together with a key sesquiterpene hydrocarbon with a novel rearranged carbon skeleton 'herbertane:'† (−)-herbertene (**1**), (−)-α-herbertenol (**2**), (−)-β-herbertenol (**3**), (−)-α-formylherbertenol (**4**), (−)-herbertenediol (**5**), and (−)-herbertenolide (**6**) in yields of 0.4, 6.2, 0.5, 0.04, 0.6, and 0.2% from the ethyl acetate extract, respectively. The present paper deals with the details of the structural determination, including the absolute configuration, and the biological activity of the new herbertane sesquiterpenoids (**1**)—(**6**).[8] These sesquiterpenoids are *ent* forms, corresponding to antipodal structures of those of higher plants, and this result is a further significant example supporting the peculiar stereospecificity in biogenesis of the liverwort sesquiterpenoids.[1-3]

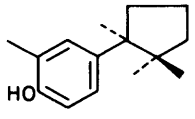
Structure of (−)-*Herbertene* (**1**).—From the least polar fraction the ethyl acetate extract a new aromatic sesquiterpene hydrocarbon which we have named (−)-herbertene (**1**), $C_{15}H_{22}$, $[\alpha]_D$ −48°, with a novel carbon skeleton was isolated. All data from the i.r., ^1H n.m.r., and ^{13}C n.m.r. spectra and from the degree of unsaturation revealed that the compound (**1**) was a bicyclic sesquiterpene hydrocarbon containing a 1,3-disubstituted benzene nucleus with a methyl group [$\nu_{max.}$ 1 610, 1 500, and 720 cm^{-1}; δ_H 6.7—7.2 (4 H, complex) and 2.34 (3 H, s); δ_C 21.8 (q), 124.2 (d), 126.2 (d), 127.4 (d), 127.9 (d), 136.8 (s), and 147.6 (s)] as well as a cyclopentane ring having three tertiary methyls [δ_H 0.58, 1.10, and 1.27 (each 3 H, s); δ_C 19.8 (t), 24.4 (q), 24.4 (q), 26.5 (q), 36.9 (t), 39.9 (t), 44.2 (s), and 50.5 (s)]. These spectroscopic properties resembled those of the known aromatic sesquiterpene cuparene (**7**), with a *para*-substitution pattern, which had been isolated as the *ent*-form from another liverwort *Bazzania pompeana* along with (−)-δ-cuparenol (**8**),[9] although aromatic sesquiterpenoids are rare in nature.[10,11] The mass fragmentation patterns of both hydrocarbons (**1**) and (**7**) were very similar. The n.m.r. signals of the new hydrocarbon (**1**) in the aromatic region (see above), however, differed appreciably from those of cuparene [δ_H 6.95 and 7.12 (each 2 H, d, *J* 8.5 Hz); δ_C 127.0 (2 d), 128.3 (2 d), 134.7 (s), and 144.6 (s)], suggesting a *meta*- or *ortho*-substitution pattern for the new compound.



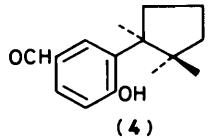
(**1**)



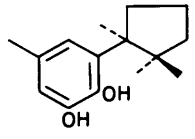
(**2**)



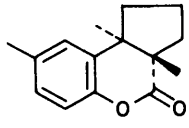
(**3**)



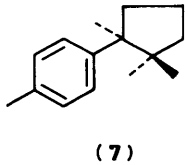
(**4**)

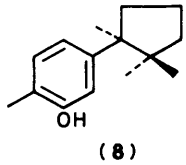


(**5**)



(**6**)


(**7**)



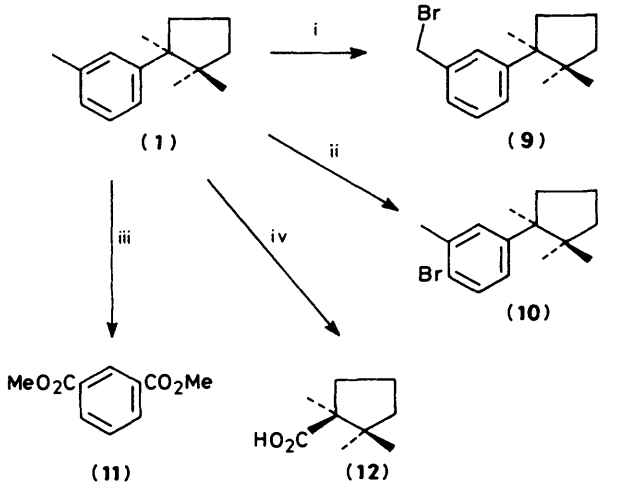
(**8**)

So, bromination of compound (**1**) was first carried out: when (**1**) was treated with bromine in carbon tetrachloride the benzyl bromide (**9**), $C_{15}H_{21}Br$ [δ_H 4.43 (2 H, s) and 7.0—7.4 (4 H)], was obtained (Scheme 1). Bromination of (**1**) with iron and iodine as catalyst, however, gave the aryl bromide (**10**), $C_{15}H_{21}Br$, which showed ^1H n.m.r. data consistent with a 1,2,4-trisubstituted benzene [δ_H 6.94 (1 H, dd, *J* 8.0 and 2.0 Hz), 7.11 (1 H, d, *J*, 2.0 Hz), and 7.32 (1 H, d, *J* 8.0 Hz)]. In order to determine the *meta*-

† We propose the name herbertane for the new carbon skeleton, and have tentatively numbered the molecule as shown in (**1**) on the basis of the numbering of the presumed biogenetic precursor *cis*-farnesyl pyrophosphate.

substitution pattern on the aromatic ring of herbertene, the aromatic hydrocarbon (**1**) was oxidized with dilute nitric acid in a sealed tube followed by methylation with diazomethane[12] to afford a dimethyl ester which was identified as dimethyl benzene-1,3-dicarboxylate (**11**) by its m.p. and spectral data, identical with those of an authentic specimen. Then, the structure and absolute configuration of the remaining cyclopentyl moiety was ascertained on the basis of the following degradation reactions: prolonged ozonolysis of the aromatic hydrocarbon (**1**) and subsequent oxidation of its ozonide with hydrogen peroxide produced the acid (**12**). The optical rotation value and spectroscopic properties coincided with those of (−)-camphonanic acid (**12**).[9,12]

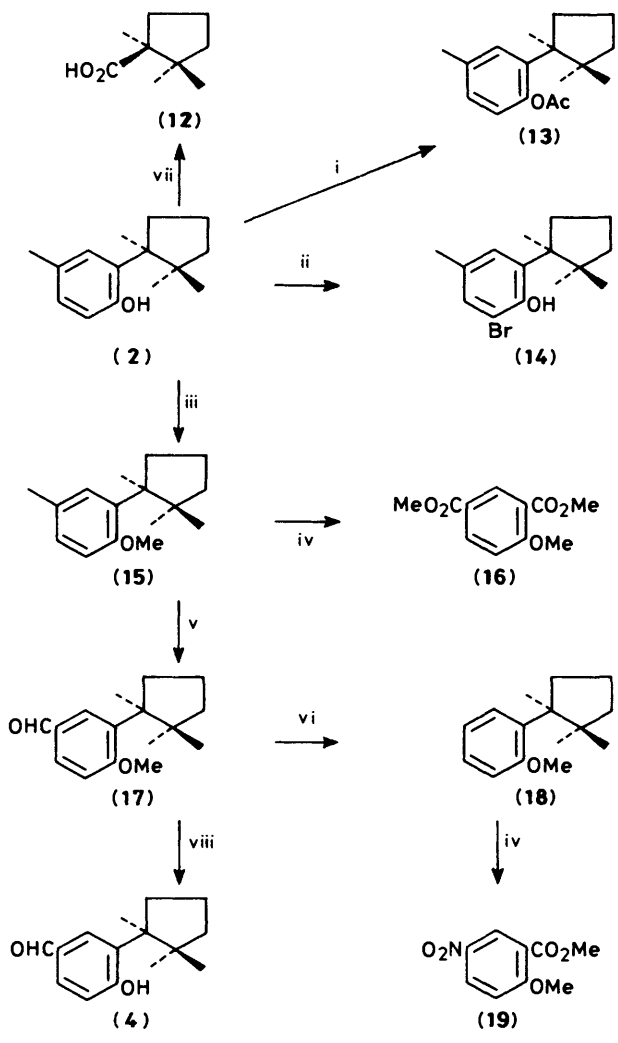
Accordingly, the structure and absolute configuration of the aromatic hydrocarbon (−)-herbertene (**1**) is represented by (1*S*)-1,2,2-trimethyl-*m*-tolylcyclopentane. The biosynthetic route to this novel carbon skeleton, enantiomeric to the configurations of higher-plant sesquiterpenoids, apparently does not follow the isoprene rule;[13] it may be formed by 1,2-methyl migration of the *ent*-cuparane skeleton produced from *cis*-farnesyl pyrophosphate through a stereospecific cyclization. Most recently, syntheses of this novel aromatic sesquiterpene have been independently performed by three research groups.[14–16]



Scheme 1. *Reagents:* i, Br_2; ii, Fe + I_2/Br_2; iii, HNO_3, CH_2N_2; iv, O_3, H_2O_2

Structure of (−)-α-*Herbertenol* (**2**).—The next less polar fraction gave the sesquiterpene phenol (−)-α-herbertenol (**2**), $C_{15}H_{22}O$, $[\alpha]_D$ −55° (3,5-dinitrobenzoate m.p. 143—144 °C), as a major constituent of the extract. The spectroscopic properties of this major compound (**2**), which produced an acetate (**13**), $C_{17}H_{24}O_2$ [$\nu_{max.}$ 1 765 cm^{-1}], suggested that it was a bicyclic sesquiterpenoid, consisting of a 2,4-disubstituted phenol [$\lambda_{max.}$ 283 and 289 nm; $\nu_{max.}$ 3 660, 3 625, 3 530, 1 610, and 1 500 cm^{-1}; δ_H 4.57 (1 H, s, exchangeable with D_2O), 6.35 (1 H, d, *J* 8.0 Hz), 6.70 (1 H, dd, *J* 8.0 and 2.0 Hz), and 6.95 (1 H, d, *J* 2.0 Hz); δ_C 116.9 (d), 127.3 (d), 128.9 (s), 130.0 (d), 133.2 (s), and 152.3 (s)], which had a different substitution pattern from the 2,5-disubstituted phenol moiety of (−)-δ-cuparenol (**8**)[9] and 3-hydroxycuparene.[17] The substituent groups on the benzene nucleus were a methyl [δ_H 2.25 (3 H, s); δ_C 20.9 (q)] and a cyclopentane ring with three tertiary methyl groups [$\nu_{max.}$ 1 385, 1 370, and 1 360 cm^{-1}; δ_H 0.75, 1.18, and 1.38 (each 3 H, s); δ_C 20.4 (t), 23.0 (q), 25.6 (q), 27.0 (q), 39.4 (t), 41.3 (t), 44.6 (s), and 51.0 (s)]. The sesquiterpene phenol (**2**) was, therefore, treated with bromine to give the aryl bromide (**14**), $C_{15}H_{21}BrO$, the ^1H n.m.r. spectrum of which showed two distinctive aromatic proton signals as a pair of doublets (*J* 2.0 Hz), at δ_H 7.00 and 7.10, which were *meta* coupling to each other. The 1,2,4-trisubstitution pattern of the original benzene nucleus was finally confirmed as that of a 2,4-disubstituted phenol by the following chemical reactions: the phenol (**2**) was converted into the methyl ether (**15**), $C_{16}H_{24}O$ [δ_H 3.74 (3 H, s)], which was then submitted to the same treatment with nitric acid followed by diazomethane, as in the case of herbertene (**1**), to produce dimethyl 4-methoxybenzene-1,3-dicarboxylate (**16**) (see Experimental section).

In order to distinguish between the two alkyl groups, the methyl ether (**15**) was oxidized with manganese dioxide to form the formyl compound (**17**), $C_{15}H_{22}O$ [$\nu_{max.}$ 1 700 cm^{-1}]. In the



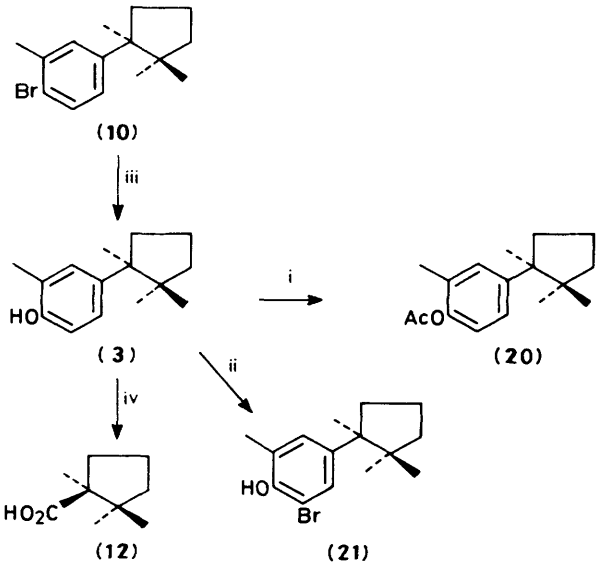
Scheme 2. *Reagents:* i, Ac_2O; ii, Br_2; iii, CH_3I; iv, HNO_3, then CH_2N_2; v, MnO_2; vi, Pd; vii, O_3, H_2O_2; viii, BBr_3

^1H n.m.r. spectrum of the aldehyde (**17**) the two aromatic protons [δ_H 7.58 (dd, *J* 8.5 and 2.0 Hz) and 7.78 (d, *J* 2.0 Hz)] with a mutual *meta* coupling between themselves suffered an anisotropic deshielding effect of the neighbouring formyl group to give a large downfield shift compared with those [δ_H 6.81 (dd, *J* 8.0 and 2.0 Hz) and 6.99 (d, *J* 2.0 Hz)] of the mother compound (**15**). The deformyl compound (**18**), $C_{15}H_{22}O$, produced by heating the formyl compound (**17**) with palladium catalyst, was submitted to nitric acid oxidation followed by methylation to afford the degradation product (**19**), $C_9H_9NO_5$,

the structure of which was identified as that of methyl 2-methoxy-5-nitrobenzoate by comparison of the physical and spectral data with those of the authentic compound prepared from salicylic acid.

The absolute configuration of the cyclopentenyl moiety was assigned on the basis of conversion of the phenol (**2**) into (−)-camphonanic acid (**12**) by ozonolysis.[9] These reactions are shown in Scheme 2.

Structures of (−)-β-*Herbertenol* (**3**) *and* (−)-α-*Formylherbertenol* (**4**).—The two compounds (−)-β-herbertenol (**3**), $C_{15}H_{22}O$, m.p. 80—81 °C, $[\alpha]_D$ −47°, and (−)-α-formylherbertenol (**4**), $C_{15}H_{20}O_2$, m.p. 134—135 °C, $[\alpha]_D$ −66°, were isolated as minor constituents, and so various chemical reactions were not performed on these compounds. The substitution pattern of the minor phenol (**3**) was recognized to be that of a 2,4-disubstituted phenol [as was the major phenol (**2**)] by analysis of the coupling pattern of the aromatic protons in the original phenol (**3**) as well as its acetate derivative (**20**), $C_{17}H_{24}O_2$, and the bromide (**21**), $C_{15}H_{21}BrO$ (see Experimental section).



Scheme 3. *Reagents:* i, Ac_2O; ii, Br; iii, BuLi, $C_6H_5NO_2$; iv, O_3, H_2O_2

Since the compound was easily deduced to be a positional isomer (with respect to the hydroxy group) of the major phenol (**2**), *i.e.* (**3**), the aryl bromide (**10**), which was previously produced from the hydrocarbon herbertene (**1**), was treated with butyl-lithium followed by nitrobenzene to give (−)-β-herbertenol (**3**) along with the mother hydrocarbon (**1**). The cyclopentenyl structure, including the stereochemistry, was confirmed by formation of (−)-camphonanic acid (**12**) (Scheme 3).

The substitution patterns of α-herbertenol (**2**) having the hydroxy group *para* to the aromatic methyl and β-herbertenol (**3**) having an *ortho* relationship between these two groups were also explainable by differences in the chemical shifts of the aromatic methyls: (a) the aromatic methyl of β-herbertenol (**3**), Δ_{Eu} 5.1 p.p.m., suffered a larger effect on addition of shift reagent Eu(dpm)$_3$* than did that of α-herbertenol (**2**), Δ_{Eu} 0.6 p.p.m. (b) The aromatic methyls *ortho* to the hydroxy groups showed resonances shifted a little upfield when the hydroxy groups were acetylated, although the aromatic methyls in *meta* and *para* relationships shifted downfield (see Table 1). (c) The difference in solvent effect of the aromatic methyls in certain acetates is shown in Table 2: the solvent effect on the aromatic methyls *ortho* to acetoxy groups was smaller than that for *meta* and *para* methyls.

* Eu(dpm)$_3$ = tris(dipivaloylmethanato)europium(III).

Table 1. Difference in ^{1}H chemical shifts of aromatic methyls between phenols and their acetate derivatives (in CCl_4)

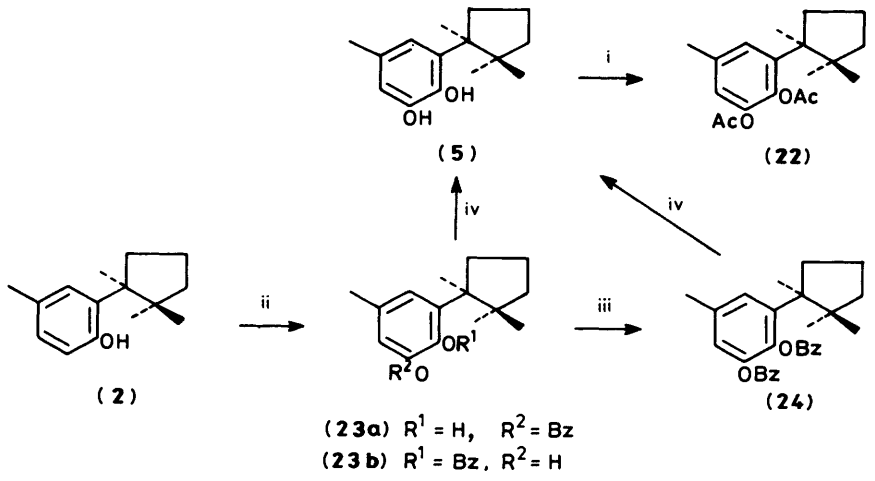
	Chemical shift of the aromatic methyl		
Phenol	δ_H(OH)	δ_H(OAc)	$\Delta[\delta_H(OH) - \delta_H(OAc)]$
α-Herbertenol (**2**)	2.25	2.30	−0.05
β-Herbertenol (**3**)	2.18	2.15	+0.03
δ-Cuparenol (**8**)	2.12	2.07	+0.05
Thymol (2-isopropyl-5-methylphenol)	2.16	2.28	−0.12
Carvacrol (5-isopropyl-2-methylphenol)	2.20	2.09	+0.11

Table 2. Solvent effect on δ_H of aromatic methyls of the acetates

	Chemical shift of the aromatic methyl		
Acetate	$\delta_H(CCl_4)$	$\delta_H(C_6H_6)$	$\Delta[\delta_H(CCl_4) - \delta_H(C_6H_6)]$
α-Herbertenol *O*-acetate (**13**)	2.30	2.13	+0.17
β-Herbertenol *O*-acetate (**20**)	2.15	2.13	+0.02
δ-Cuparenol *O*-acetate	2.07	2.04	+0.03
'Thymyl acetate'	2.28	2.06	+0.22
'Carvacryl acetate'	2.09	2.06	+0.03

Similarly the spectroscopic properties of (−)-α-formylherbertenol (**4**) suggested the presence of a 1,2,4-trisubstituted benzene nucleus with a formyl group, a hydroxy group, and a cyclopentenyl residue. The spectra, especially the ^{1}H n.m.r. spectrum, were similar to those of the formyl compound (**17**) prepared from the major metabolite α-herbertenol (**2**). Indeed, the physical and spectral data of (−)-α-formylherbertenol (**4**) were coincident with those of compound (**4**) derived from the methyl ether (**17**) by treatment with boron tribromide.

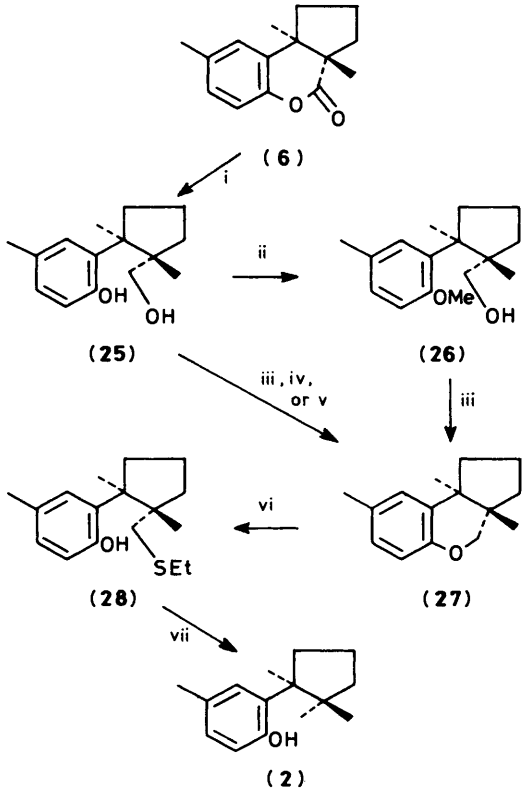
Structures of (−)-*Herbertenediol* (**5**) *and* (−)-*Herbertenolide* (**6**).—The fifth compound, (−)-herbertenediol (**5**), $C_{15}H_{22}O_2$, m.p. 90—91 °C, $[\alpha]_D$ −47°, which gave a diacetate (**22**), $C_{19}H_{26}O_4$, was isolated as a sesquiterpene diphenol. The ^{1}H n.m.r. spectrum of the compound was similar to those of the herbertenols described above in the chemical shift of the methyl signals. However, the aromatic protons appeared as only two signals [δ_H 6.39 and 6.58 (each 1 H, br s)], suggesting a *meta* relationship of the two protons. The substitution pattern of the two hydroxy groups was, furthermore, recognized as the catechol type since the u.v. spectrum underwent a bathochromic shift (9 nm) on addition of boric acid and sodium acetate.[18] On the basis of the similarities of the chemical shifts of the tertiary methyls [δ_H 0.75, 1.18, and 1.38] to those [δ_H 0.75, 1.18, and 1.38] of (−)-α-herbertenol (**2**), the structure of the diol was deduced to be a hydroxy derivative of α-herbertenol, that is, structure (**5**). (−)-α-Herbertenol (**2**) was, therefore, submitted to benzoyloxylation with benzoyl peroxide to afford the (1:1) benzoyloxyphenol mixture (**23a** and **b**).[19,20] The mixture (**23a** and **b**) was then esterified with benzoyl chloride to give the single dibenzoate (**24**), $C_{29}H_{30}O_4$, treatment of which with lithium aluminium hydride produced the diol (**5**), $C_{15}H_{22}O_2$.



Scheme 4. *Reagents:* i, Ac_2O; ii, $(BzO)_2$; iii, BzCl; iv, $LiAlH_4$

This diol (**5**) was also formed through the same reduction of the isomers (**23a** and **b**) (Scheme 4). The optical rotation and the spectral data of (−)-herbertenediol (**5**) were in good agreement with those of the diol derived from (−)-α-herbertenol (**2**) by the above chemical reactions. The structure, including the absolute configuration, of (−)-herbertenediol is, therefore, represented by formula (**5**).

(−)-Herbertenolide (**6**), $C_{15}H_{18}O_2$, m.p. 95.5—96.5 °C, $[\alpha]_D$ 86°, was shown by its spectroscopic properties to be a tricyclic sesquiterpenoid containing a six-membered phenolic lactone ring [$\nu_{max.}$ 1 770 cm^{-1}], a trisubstituted benzene ring with a methyl group [δ_H 2.33 (3 H, s) and 6.7—7.1 (3 H, complex)], and two tertiary methyl groups [δ_H 0.90 and 1.11 (each 3 H, s)], suggesting a lactone derivative of the above herbertenoids. Reduction of the δ-lactone (**6**) with lithium aluminium hydride gave the hydroxyphenol (**25**), $C_{15}H_{22}O_2$, having a primary hydroxy group. For the purpose of transformation of the diol (**25**) into herbertenol (**2**) or (**3**) by removal of the primary hydroxy group, the hydroxyphenol (**25**) and its methyl ether (**26**), $C_{16}H_{24}O_2$, were respectively treated with triphenyl phosphite methiodide in hexamethylphosphoric triamide (HMPA)[21] and the mixture was then heated with sodium cyanoborohydride.[22] Nevertheless, they did not give any phenols, or even any alkyl iodides, but instead formed the six-membered cyclic ether (**27**), $C_{15}H_{20}O$. Formation of this ether (**27**) arose easily from the hydroxyphenol (**25**) by treatment with only triphenyl phosphite methiodide in HMPA. Even refluxing the diol (**25**) with benzene containing a catalytic amount of toluene-*p*-sulphonic acid (PTSA) produced the cyclic ether (**27**). Next, when the cyclic ether (**27**) was subjected to reaction with aluminium trichloride and ethanethiol,[23] the hydroxy thioether (**28**), $C_{17}H_{26}OS$, was fortunately produced in a higher yield (see Scheme 5). Then, formation of the phenol (**2**), $C_{15}H_{22}O$, was achieved by reduction of the hydroxy thioether (**28**) with Raney nickel. The spectra and optical rotation of the product were identical with those of (−)-α-herbertenol (**2**). Finally, determination of the stereochemistry of the lactone ring was based on examination of the chemical shifts of the tertiary methyls in the diol (**25**) and the methyl ether (**26**) prepared from the lactone (**6**): one methyl group [δ_H 0.80 in (**25**) and 0.64 in (**26**)] resonated at high field, and the δ_H value was analogous to that of one methyl signal [δ_H 0.75 in (**2**) and 0.67 in (**15**)] of the three tertiary methyls groups in (−)-α-herbertenol (**2**) and its methoxy derivative (**15**). These methyl groups, shielded by the



Scheme 5. *Reagents:* i, $LiAlH_4$; ii, CH_3I; iii, $(PhO)_3PCH_3I$, $NaBH_3CN$; iv, *p*-$CH_3C_6H_4SO_2H$–C_6H_6; v, $(PhO)_3PCH_3I$; vi, $AlCl_3$, EtSH; vii, Ni(H)

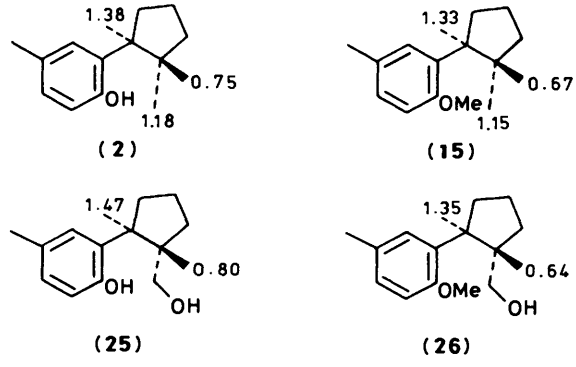


Table 3. Growth-inhibitory effect (percentage inhibition) of the herbertane sesquiterpenoids on mycelial growth of the pathogenic fungi

Compound	Pathogenic fungus	Concentration (p.p.m.) 0.1	1	10	100	I_{50} (p.p.m.)
α-Herbertenol (**2**)	*B. cinerea*	10	13	38	100	20
	R. solani	3	7	30	80	25
	P. debaryanum	0	0	15	67	60
β-Herbertenol (**3**)	*B. cinerea*	0	13	38	83	20
	R. solani	8	10	55	100	8
	P. debaryanum	0	0	15	80	40
α-Formylherbertenol (**4**)	*B. cinerea*	8	13	56	—	8
	R. solani	0	10	53	—	10
	P. debaryanum	0	0	0	—	
β-Bromoherbertenol (**21**)	*B. cinerea*	0	6	42	—	*ca.* 15
	R. solani	0	0	13	—	
	P. debaryanum	0	0	0	—	

anisotropic effect of the benzene ring, have been determined to be β-configurational methyl groups in a *cis*-relationship with the benzene nucleus.[24,25]

Accordingly, the structure of (−)-herbertenolide was assigned as (**6**).

Biological Activity.—The growth-inhibitory activity of the herbertenoids (−)-α-herbertenol (**2**), (−)-β-herbertenol (**3**), (−)-α-formylherbertenol (**4**), and (−)-β-bromoherbertenol (**21**) was tested on some plant pathogenic fungi. As shown in Table 3, the percentage inhibition of the herbertenoids was determined at concentrations of 0.1, 1, 10, and 100 p.p.m. Their 50% growth inhibition concentration (I_{50}) was also obtained. These four compounds are strong inhibitors of *Botrytis cinerea* and *Rhizoctonia solani.*

Experimental

M.p.s are uncorrected. Optical rotations were taken on an automatic polarimeter in chloroform solutions at 25 °C, and u.v. spectra were measured in ethanol solutions. I.r. spectra were recorded in carbon tetrachloride solutions on a grating spectrometer. Unless stated otherwise, ^{1}H n.m.r. (60 or 90 MHz) spectra were measured for carbon tetrachloride solutions and ^{13}C n.m.r. (22.63 MHz) spectra for deuteriochloroform solutions with tetramethylsilane as internal standard. The chemical shifts are presented in terms of δ values. Mass spectra were determined at 70 eV. For column chromatography Merck Kieselgel 60 was used and Merck Kieselgel 60 PF_{254} was used for t.l.c. and p.l.c. Analytical plates were visualized under u.v. light, with iodine vapour, or by spraying with 10% sulphuric acid in ethanol followed by heating at 120 °C.

Material and its Extraction.—The liverwort, *Herberta adunca*, was collected in a forest at Motoyama-cho in Kochiken, Shikoku. The whole plant (3.60 kg), after being washed with water and dried in the shade for several days, was digested twice with methanol for a week at room temperature. The solvent was distilled off under reduced pressure and the oily material thus obtained was again extracted with ethyl acetate. Removal of the solvent under reduced pressure gave a viscous oily substance (113.4 g).

Isolation of the Constituents (**1**)—(**6**).—The ethyl acetate extract (24.0 g) was first chromatographed through a column packed with silica gel (600 g), with hexane containing increasing proportions of ethyl acetate as eluant, into several fractions. Each fraction was then subjected to a further combination of column chromatography and p.l.c. on silica gel to isolate the following compounds in order of elution: (−)-herbertene (**1**) (96 mg), (−)-α-herbertenol (**2**) (1.49 g), (−)-herbertenolide (**6**) (48 mg), (−)-β-herbertenol (**3**) (120 mg), (−)-herbertenediol (**5**) (144 mg), and (−)-α-formylherbertenol (**4**) (10 mg). The physical properties and spectroscopic data of these compounds are listed below.

(−)-*Herbertene* [*herberta*-1,3,5-*triene*] (**1**). Gum; $[\alpha]_D$ −48.3° (*c* 1.3) (Found: C, 89.0; H, 11.0. $C_{15}H_{22}$ requires C, 88.74; H, 11.24%); $\nu_{max.}$ 1 610, 1 500, 1 390, 1 380, 1 370, and 720 cm^{-1}; δ_H 0.58, 1.10, 1.27, and 2.34 (each 3 H, s), and 6.7—7.2 (4 H, complex); δ_C 147.6 (s), 136.8 (s), 127.9 (d), 127.4 (d), 126.2 (d), 124.2 (d), 50.5 (s), 44.2 (s), 39.9 (t), 36.9 (t), 26.5 (q), 24.4 (q), 24.4 (q), 21.8 (q), and 19.8 (t); *m/z* (rel. int.) 202 (M^+, 42%), 187 (7), 159 (19), 145 (32), 132 (100), 120 (41), 105 (21), 91 (14), 83 (7), 77 (6), 69 (7), 51 (9), and 41 (19).

(−)-α-*Herbertenol* [1-*hydroxyherbertene*] (**2**). Gum; $[\alpha]_D$ −55.0° (*c* 1.8) (Found: C, 82.5; H, 10.3. $C_{15}H_{22}O$ requires C, 82.51; H, 10.16%); $\nu_{max.}$ 3 660, 3 625, 3 520, 1 605, 1 500, 1 402, 1 385, 1 370, 1 360, 1 240, 1 170, 1 150, 930, 880, and 823 cm^{-1}; δ_H 0.75, 1.18, 1.38, and 2.25 (each 3 H, s), 4.57 (1 H, s, exchangeable with D_2O), 6.35 (1 H, d, *J* 8.0 Hz), 6.70 (1 H, dd, *J* 8.0 and 2.0 Hz), and 6.95 (1 H, d, *J* 2.0 Hz); δ_C 152.3 (s), 133.2 (s), 130.0 (d), 128.9 (s), 127.3 (d), 116.9 (d), 51.0 (s), 44.6 (s), 41.3 (t), 39.4 (t), 27.0 (q), 25.6 (q), 23.0 (q), 20.9 (q), and 20.4 (t); $\lambda_{max.}$ 220, 283, and 289 nm (ε 5 250, 2 540, and 2 300); *m/z* 218 (M^+, 76%), 203 (6), 175 (9), 161 (33), 148 (100), 135 (84), 121 (28), 105 (19), 91 (18), 79 (61), 69 (9), 53 (27), and 41 (24).

(−)-β-*Herbertenol* [3-*hydroxyherbertene*] (**3**). M.p. 80—81 °C (from hexane); $[\alpha]_D$ −47.0° (*c* 0.7) (Found: C, 82.4; H, 10.5. $C_{15}H_{22}O$ requires C, 82.51; H, 10.16%); $\nu_{max.}$ 3 630, 3 470, 1 610, 1 600, 1 505, 1 385, 1 375, 1 365, 1 325, 1 310, 1 260, 1 112, 997, and 828 cm^{-1}; δ_H 0.56, 1.03, 1.22, and 2.18 (each 3 H, s), 4.48 (1 H, br s, exchangeable with D_2O), 6.48 (1 H, d, *J* 8.0 Hz), 6.87 (1 H, dd, *J* 8.0 and 2.0 Hz), and 6.97 (1 H, d, *J* 2.0 Hz); $\lambda_{max.}$ 225, 277, and 284 nm (ε 5 170, 1 500, and 1 380); *m/z* 218 (M^+, 56%), 203 (12), 175 (8), 161 (58), 148 (100), 135 (63), 121 (19), 105 (9), 91 (18), 77 (15), 69 (22), 55 (22), and 41 (35).

(−)-α-*Formylherbertenol* [1-*hydroxy*-12-*oxoherbertene*] (**4**). M.p. 134—135 °C (from hexane–chloroform); $[\alpha]_D$ −65.8° (*c* 0.4) (Found: C, 77.8; H, 8.7. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68%); $\nu_{max.}$ 3 620, 3 320, 1 698, 1 675, 1 590, 1 510, 1 425, 1 375, 1 220, 1 150, 1 105, and 1 060 cm^{-1}; δ_H 0.75, 1.22, and 1.43 (each 3 H, s), 6.97 (1 H, d, *J* 8.0 Hz), 7.58 (1 H, dd, *J* 8.0 and 2.0 Hz), 7.85 (1 H, d, *J* 2.0 Hz), 8.40 (1 H, br s, exchangeable with D_2O), and 9.76 (1 H, s); $\lambda_{max.}$ 292 nm (ε 11 000); *m/z* 232 (M^+, 34%), 217 (7), 215 (5), 210 (3), 203 (4), 189 (8), 174 (16), 162 (100), 149 (52), 132 (18), 121 (15), 105 (12), 91 (19), 83 (14), 77 (18), 69 (23), 55 (24), and 41 (27).

(−)-*Herbertenediol* [1,2-*dihydroxyherbertene*] (**5**). M.p. 90—91 °C (from hexane); $[\alpha]_D$ −46.5° (*c* 1.4) (Found: C, 76.6; H, 9.8. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%); $\nu_{max.}$ 3 630, 3 570, 3 410, 1 600, 1 495, 1 384, 1 372, 1 363, 1 293, 1 230, 1 165, and 980 cm^{-1}; δ_H 0.75, 1.18, 1.38, and 2.18 (each 3 H, s), 5.28 (2 H, br s, exchangeable with D_2O), 6.39 (1 H, br s), and 6.58 (1 H, br s); $\lambda_{max.}$ 285 nm (ε 3 100); $\lambda_{max.}$ (EtOH–H_3BO_4–NaOAc) 294 nm (ε 6 300); *m/z* 234 (M^+, 84%), 219 (3), 191 (4), 178 (7), 164 (59), 152 (100), 151 (98), 137 (18), 115 (6), 105 (6), 91 (11), 77 (9), 69 (10), 55 (9), 47 (44), and 41 (18).

(−)-*Herbertenolide* [14,1-*herbertenolide*] (**6**). M.p. 95.5—96.5 °C (from hexane); $[\alpha]_D$ −86.4° (*c* 1.3) (Found: C, 78.0; H, 8.1. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%); $\nu_{max.}$ 1 770, 1 490, 1 379, 1 270, 1 200, 1 125, 1 090, 1 055, and 934 cm^{-1}; δ_H 0.90, 1.11, and 2.33 (each 3 H, s) and 6.7—7.1 (3 H, complex); δ_H (C_6H_6) 0.70, 0.94, and 2.09 (each 3 H, s); $\lambda_{max.}$ 230.5, 272, and 279 nm (ε 6 460, 1 120, and 1 010); *m/z* 230 (M^+, 89%), 215 (57), 202 (39), 187 (100), 173 (17), 159 (53), 145 (22), 134 (13), 121 (15), 115 (15), 105 (13), 91 (18), 79 (17), 69 (12), 55 (15), and 41 (23).

Bromination of (−)-*Herbertene* (**1**).—(*a*) A solution of bromine in carbon tetrachloride was slowly added to a stirred solution of the hydrocarbon (**1**) (34 mg) in carbon tetrachloride (2 ml). After 12 h, the reaction mixture was diluted with the same solvent, washed with water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a product which was purified by p.l.c. (hexane) to provide the benzyl bromide (**9**) (19 mg), along with recovered starting material (**1**) (18 mg).

(*b*) Catalytic amounts of iron powder and iodine were added to a solution of (−)-herbertene (**1**) (24 mg) in carbon tetrachloride (2 ml) and the solution was cooled in an ice-bath. A solution of bromine (50 mg) in the same solvent (0.4 ml) was added dropwise to the solution and the mixture was stirred for 2 h, diluted with chloroform, and the organic layer was washed successively with water, 5% aqueous sodium hydrogen sulphite, and water. After the solution had been dried ($MgSO_4$) the solvent was distilled off under reduced pressure to yield a crude product. The aryl bromide (**10**) (32 mg) was purified by p.l.c. (hexane).

12-*Bromoherbertene* (**9**). Gum; $[\alpha]_D$ −39.4° (*c* 1.0) (Found: C, 63.8; H, 7.7. $C_{15}H_{21}Br$ requires C, 64.06; H, 7.53%); $\nu_{max.}$ 1 610, 1 490, 1 390, 1 380, 1 370, and 710 cm^{-1}; δ_H 0.58, 1.10, and 1.30 (each 3 H, s), 4.43 (2 H, s), and 7.0—7.4 (4 H, complex); *m/z* 282, 280 (M^+, 18, 19%), 212 (32), 210 (33), 201 (36), 145 (41), 131 (100), 119 (24), 105 (8), 91 (23), 83 (17), 69 (12), 55 (17), and 41 (22).

3-*Bromoherbertene* (**10**). M.p. 78.5—79.5 °C (from hexane); $[\alpha]_D$ −51.5° (*c* 1.3) (Found: C, 63.9; H, 7.7%); $\nu_{max.}$ 1 490, 1 395, 1 380, 1 370, 1 040, 727, 692, and 675 cm^{-1}; δ_H 0.59, 1.09, 1.29, and 2.40 (each 3 H, s), 6.94 (1 H, dd, *J* 8.0 and 2.0 Hz), 7.11 (1 H, d, *J* 2.0 Hz), and 7.32 (1 H, d, *J* 8.0 Hz); *m/z* 282, 280 (M^+, 31, 29%), 267 (3), 265 (3), 239 (1), 237 (1), 225 (4), 223 (4), 212 (97), 210 (100), 199 (19), 197 (21), 185 (7), 183 (7), 158 (7), 145 (48), 130 (20), 119 (14), 115 (17), 105 (4), 91 (11), 83 (9), 69 (6), 55 (34), and 41 (12).

Oxidation of (−)-*Herbertene* (**1**) *with Nitric Acid followed by Methylation with Diazomethane.*—The hydrocarbon (**1**) (55 mg) and 30% nitric acid (0.7 ml) were sealed in a glass tube (1.8 × 13 cm, thickness 1.5 mm), and the tube was heated for 9 h at 170 °C.[9,12] After the tube had been cooled and opened, the reaction mixture was filtered to obtain crystals which were dissolved in methanol. An ethereal solution of diazomethane was added and the mixture was kept for 4 h before being worked up by the usual way, and the dimethyl ester (**11**) (8 mg) was purified by p.l.c. [hexane–ethyl acetate (4:1)]. Dimethyl isophthalate (**11**) had m.p. 64—65 °C (from hexane)* (lit.,[26] 67.6—68.2 °C); $\nu_{max.}$ 1 740, 1 440, 1 320, 1 250, and 740 cm^{-1}; δ_H 3.93 (6 H, s), 7.45 (2 H, dd, *J* 8.0 and 8.0 Hz), 8.13 (1 H, dd, *J* 8.0 and 2.0 Hz), and 8.53 (1 H, dd, *J* 2.0 and 2.0 Hz); *m/z* 194 (M^+, 30%), 163 (100), 135 (29), 120 (9), 103 (13), 92 (4), 76 (18), 66 (7), and 50 (12).

Ozonolysis of (−)-*Herbertene* (**1**).—Into a solution of the hydrocarbon (**1**) (52 mg) in ethyl acetate (10 ml) cooled in an ice-bath was bubbled ozonized oxygen for 12 h. After removal of the excess of gas by blowing nitrogen gas through the solution, the solvent was distilled off under reduced pressure. The ozonide was heated with 35% hydrogen peroxide (0.3 ml) and 5% aqueous sodium hydroxide (3 ml) on a steam-bath for 2 h.[9,12] The reaction mixture was acidified by 5% hydrochloric acid and extracted with chloroform. (−)-Camphonanic acid (**12**) (17 mg) was isolated as crystals by p.l.c. [hexane–acetone (2:1)]. (−)-Camphonanic acid (**12**) had m.p. 188—189 °C (sealed tube) (from hexane) [lit.,[9] 190 °C; lit.[12] (enantiomer) 191—192 °C]; $[\alpha]_D$ −15.6° (*c* 0.5) [lit.,[9] −13.2°; lit.,[12] (enantiomer) +21°]; $\nu_{max.}$ 3 500—2 500, 1 700, 1 408, 1 388, 1 375, 1 368, 1 298, and 1 107 cm^{-1}; δ_H 0.99, 1.07, and 1.19 (each 3 H, s), and 11.92 (1 H, br s, exchangeable with D_2O); *m/z* 156 (M^+, 3%), 138 (16), 106 (5), 95 (13), 87 (52), 83 (16), 70 (100), 55 (32), and 43 (12).

Preparation of the 3,5-*Dinitrobenzoate of* (−)-α-*Herbertenol* (**2**).—The phenol (**2**) (24 mg) and 3,5-dinitrobenzoyl chloride (32 mg) were stirred in pyridine (1 ml) for 11 h at 70 °C. After being cooled and diluted with ether, the solution was treated in the usual way to afford a crude product which was purified by p.l.c. [hexane–ethyl acetate (20:1)] to yield the 3,5-dinitrobenzoate (19 mg) as crystals, along with recovered starting material (**2**) (14 mg).

1-(3,5-*Dinitrobenzoyloxy*)*herbertene.* M.p. 143—144 °C (from hexane–chloroform); $[\alpha]_D$ −2.0° (*c* 1.0) (Found: C, 63.95; H, 6.0; N, 6.9. $C_{22}H_{24}N_2O_6$ requires C, 64.06; H, 5.87; N, 6.79%); $\nu_{max.}$ 1 760, 1 643, 1 550, 1 350, 1 270, 1 165, 1 083, 935, and 730 cm^{-1}; δ_H 0.80, 1.15, 1.28, and 2.39 (each 3 H, s), 6.82 (1 H, d, *J* 8.0 Hz), 7.02 (1 H, dd, *J* 8.0 and 2.0 Hz), 7.28 (1 H, d, *J* 2.0 Hz), and 9.21 (3 H, s); *m/z* 412 (M^+, 9%), 342 (8), 329 (25), 279 (14), 217 (12), 195 (44), 175 (8), 167 (34), 149 (96), 135 (19), 117 (16), 103 (9), 83 (20), 75 (27), 70 (23), 55 (100), and 41 (44).

Acetylation of (−)-α-*Herbertenol* (**2**).—A solution of the phenol (**2**) (27 mg) in acetic anhydride (0.5 ml)–pyridine (0.3 ml) was stirred overnight at room temperature, and the mixture was then extracted with ether. The product, recovered in the usual way, was purified by p.l.c. [hexane–acetone (9:1)] to give the acetate (**13**) (31 mg) as a gum.

(−)-α-*Herbertenol O-acetate* [1-*acetoxyherbertene*] (**13**). $[\alpha]_D$ −45.8° (*c* 1.2) (Found: C, 78.7; H, 9.6. $C_{17}H_{24}O_2$ requires C, 78.42; H, 9.29%); $\nu_{max.}$ 1 765, 1 493, 1 387, 1 367, 1 210, 1 205, and 910 cm^{-1}; δ_H 0.72, 1.13, 1.27, 2.17, and 2.30 (each 3 H, s), 6.67 (1 H, d, *J* 8.0 Hz), 6.88 (1 H, dd, *J* 8.0 and 2.0 Hz), and 7.10 (1 H, d, *J* 2.0 Hz); *m/z* 260 (M^+, 38%), 245 (2), 218 (94), 203 (6), 186 (3), 177 (16), 161 (32), 148 (100), 135 (64), 91 (18), 77 (13), 69 (18), 55 (13), and 43 (52).

Bromination of (−)-α-*Herbertenol* (**2**).—The phenol (**2**) (31 mg) was dissolved in carbon tetrachloride (1 ml) and was treated dropwise with a 10% solution of bromine in the same solvent until the bromine colour persisted. The mixture was stirred for 3 h at room temperature and worked up by the usual way. The bromide (**14**) (39 mg) was purified by p.l.c. [hexane–benzene (10:1)].

* The above m.p. and spectral data were coincident with those of dimethyl isophthalate (m.p. 64—65 °C; from hexane) prepared from isophthalic acid.

(−)-α-*Bromoherbertenol* [2-*bromo*-1-*hydroxyherbertene*] (**14**). Gum; $[\alpha]_D$ −56.3° (*c* 1.1) (Found: C, 60.6; H, 7.3. $C_{15}H_{21}BrO$ requires C, 60.61; H, 7.12%); $\nu_{max.}$ 3 550, 1 570, 1 470, 1 390, 1 375, 1 365, 1 338, 1 270, 1 243, 1 208, 1 170, 1 140, and 860 cm^{-1}; δ_H 0.75, 1.22, 1.38, and 2.23 (each 3 H, s), 5.49 (1 H, br s, exchangeable with D_2O), and 7.00 and 7.10 (each 1 H, d, *J* 2.0 Hz); *m/z* 298, 296 (M^+, 49, 53%), 283 (4), 281 (4), 255 (4), 253 (4), 240 (11), 228 (96), 226 (100), 215 (67), 213 (69), 201 (16), 199 (16), 174 (12), 160 (56), 146 (50), 132 (26), 115 (18), 103 (12), 91 (22), 83 (40), 69 (24), 55 (32), and 41 (29).

Methylation of (−)-α-*Herbertenol* (**2**).—Methyl iodide (475 mg) and potassium carbonate (480 mg) were added to a dry acetone solution of the phenol (**2**) (375 mg in 10 ml). After being heated under reflux for 6 h and then cooled, the reaction mixture was filtered and the filtrate was treated in the usual way to afford crude products which were purified by column chromatography [hexane–benzene (9:1)] to yield the methyl ether (**15**) (263 mg) as a gum, along with recovered starting material (**2**) (116 mg).

1-*Methoxyherbertene* (**15**). $[\alpha]_D$ −56.3° (*c* 2.5) (Found: C, 82.9; H, 10.7. $C_{16}H_{24}O$ requires C, 82.70; H, 10.41%); $\nu_{max.}$ 1 605, 1 580, 1 500, 1 465, 1 385, 1 370, 1 365, 1 285, 1 245, 1 073, and 1 045 cm^{-1}; δ_H 0.67, 1.15, 1.33, 2.26, and 3.74 (each 3 H, s), 6.62 (1 H, d, *J* 8.0 Hz), 6.81 (1 H, dd, *J* 8.0 and 2.0 Hz), and 6.99 (1 H, d, *J* 2.0 Hz); *m/z* 232 (M^+, 83%), 217 (12), 204 (2), 201 (3), 189 (8), 175 (39), 162 (80), 149 (100), 135 (36), 119 (24), 110 (28), 105 (19), 95 (16), 91 (20), 83 (9), 77 (12), 69 (13), 55 (12), and 41 (21).

Nitric Acid Oxidation of the Methyl Ether (**15**) *followed by Methylation with Diazomethane.*—The methyl ether (**15**) (146 mg) and 20% nitric acid (2 ml) were heated in a sealed tube (1.8 × 13 cm, thickness 1.5 mm) for 17 h at 165 °C. The white crystalline material obtained was collected by filtration, washed with water, and treated with an ethereal solution of diazomethane to give a product which was purified by p.l.c. [benzene–ethyl acetate (9:1)] to afford the derivative of dimethyl terephthalate, (**16**) (6 mg), as crystals. Dimethyl 4-methoxybenzene-1,3-dicarboxylate (**16**) had m.p. 97.5—98.5 °C (from hexane–chloroform)* (lit.,[27] 95—96 °C); $\nu_{max.}$ 1 730, 1 610, 1 505, 1 465, 1 435, 1 275, 1 235, 1 160, 1 135, 1 095, 1 035, and 1 000 cm^{-1}; δ_H 3.88 (6 H, s), 3.95 (3 H, s), 6.93 (1 H, d, *J* 8.5 Hz), 8.04 (1 H, dd, *J* 8.5 and 2.0 Hz), and 8.35 (1 H, d, *J* 2.0 Hz); *m/z* 224 (M^+, 31%), 193 (100), 191 (34), 179 (2), 165 (7), 150 (9), 135 (11), 127 (15), 119 (12), 103 (7), 95 (6), 76 (9), 59 (6), and 43 (14).

Manganese Dioxide Oxidation of the Methyl Ether (**15**).—A mixture of the methyl ether (**15**) (290 mg), manganese dioxide (0.6 g), and 30% sulphuric acid (5 ml) was stirred vigorously for 8.5 h at 62 °C.[28] After having cooled, the mixture was extracted with ether and the extract was worked up in the usual way to yield a crude product. The aldehyde (**17**) (159 mg) was purified by p.l.c. [hexane–ether (4:1)].

1-*Methoxy*-12-*oxoherbertene* (**17**). Gum $[\alpha]_D$ −64.5° (*c* 1.4) (Found: C, 77.7; H, 9.3. $C_{16}H_{22}O_2$ requires C, 78.01; H, 9.00%); $\nu_{max.}$ 2 750, 1 700, 1 600, 1 580, 1 500, 1 390, 1 375, 1 370, 1 260, 1 215, 1 185, 1 160, and 1 040 cm^{-1}; δ_H 0.67, 1.17, 1.36, and 3.87 (each 3 H, s), 6.89 (1 H, d, *J* 8.5 Hz), 7.58 (1 H, dd, *J* 8.5 and 2.0 Hz), 7.78 (1 H, d, *J* 2.0 Hz), and 9.78 (1 H, s); *m/z* 246 (M^+, 63%), 231 (12), 215 (54), 203 (7), 188 (13), 176 (70), 163 (86), 161 (100), 147 (27), 133 (31), 115 (20), 105 (40), 91 (34), 83 (19), 77 (22), 69 (6), 55 (26), and 41 (37).

Decarbonylation of the Aldehyde (**17**).—The aldehyde (**17**) (145 mg) and palladium–carbon powder (10% palladium) (5 mg) were heated under nitrogen for 1.5 h at 200—210 °C.[29] After having cooled, the reaction mixture was dissolved in ether and the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to afford a gum which was purified by p.l.c. [hexane–acetone (9:1)] to give the norsesquiterpenoid (**18**) (107 mg) as a gum, along with the recovered starting material (**17**) (7 mg).

1-*Methoxy*-12-*norherbertene* (**18**). $[\alpha]_D$ −66.1° (*c* 2.2) (Found: C, 82.6; H, 10.15. $C_{15}H_{22}O$ requires C, 82.51; H, 10.16%); $\nu_{max.}$ 1 600, 1 580, 1 490, 1 465, 1 450, 1 430, 1 385, 1 370, 1 360, 1 290, 1 240, 1 190, and 1 040 cm^{-1}; δ_H 0.68, 1.16, 1.36, and 3.76 (each 3 H, s) and 6.5—7.4 (4 H, complex); *m/z* 218 (M^+, 66%), 203 (11), 187 (3), 175 (11), 161 (40), 148 (88), 135 (100), 133 (75), 121 (35), 110 (32), 105 (41), 95 (14), 91 (38), 83 (17), 77 (23), 69 (12), 55 (22), and 41 (35).

Nitric Acid Oxidation of the Norether (**18**) *followed by Treatment with Diazomethane.*—The methyl ether (**18**) (95 mg) and 20% nitric acid (1 ml) were heated in a sealed tube for 11 h at 160 °C. After the tube had cooled and been opened, the reaction mixture was extracted with chloroform, and the extract was washed successively with water and saturated aqueous sodium chloride and dried ($MgSO_4$). After evaporation of the solvent, the residue was dissolved with ether and treated with a solution of diazomethane in ether. Purification by p.l.c. [hexane–ethyl acetate (4:1)] provided the benzoate derivative (**19**) (10 mg) as crystals. Methyl 2-methoxy-5-nitrobenzenoate (**19**) had m.p. 101—102 °C (from hexane–chloroform)† (lit.,[30] 99—100 °C); $\nu_{max.}$ 1 743, 1 725, 1 615, 1 590, 1 523, 1 492, 1 462, 1 434, 1 345, 1 280, 1 250, 1 135, 1 083, and 1 031 cm^{-1}; δ_H 3.91 and 4.03 (each 3 H, s), 7.03 (1 H, d, *J* 9.0 Hz), 8.31 (1 H, dd, *J* 9.0 and 2.5 Hz), and 8.59 (1 H, d, *J* 2.5 Hz); *m/z* 211 (M^+, 48%), 196 (9), 180 (100), 165 (4), 150 (24), 134 (55), 122 (8), 107 (8), 91 (6), 76 (29), 63 (15), and 55 (11).

Ozonolysis of (−)-α-*Herbertenol* (**2**).—The phenol (**2**) (32 mg) was dissolved in ethyl acetate (7 ml) and ozonized for 2 h at −65 °C; the ozonide was decomposed in the same way as for the ozonolysis of herbertene by use of hydrogen peroxide. The usual work-up gave the acid (**12**) (6 mg) as crystals. The m.p. (189—190 °C, sealed tube), optical rotation ($[\alpha]_D$ −13.0°, *c* 0.7), and spectral data (i.r., ^1H n.m.r., and m.s.) of this compound were identical in all respects with those of (−)-camphonanic acid (**12**).

Acetylation of (−)-β-*Herbertenol* (**3**).—A mixture of the phenol (**3**) (24 mg), acetic anhydride (1 ml), and pyridine (0.5 ml) was stirred for 5 h at room temperature. The product, obtained in the usual manner, was purified by p.l.c. [hexane–acetone (20:1)], yielding the acetate (**20**) (26 mg) as crystals.

(−)-β-*Herbertenol O-acetate* [3-*acetoxyherbertene*] (**20**). M.p. 33—34 °C (from hexane); $[\alpha]_D$ −50.9° (*c* 0.8) (Found: C, 78.6; H, 9.6. $C_{17}H_{24}O_2$ requires C, 78.42; H, 9.29%); $\nu_{max.}$ 1 769, 1 502, 1 369, 1 205, 1 125, 1 017, and 912 cm^{-1}; δ_H 0.58, 1.05, 1.28, 2.15, and 2.25 (each 3 H, s), 6.77 (1 H, d, *J* 9.0 Hz), 7.08 (1 H, br d, *J* 9.0 Hz), and 7.08 (1 H, br s); *m/z* 260 (M^+, 36%), 218 (87), 203 (9), 180 (9), 175 (4), 161 (39), 148 (100), 135 (41), 121 (10), 105 (5), 91 (11), 77 (7), 69 (11), 53 (4), and 43 (22).

Bromination of (—)-β-*Herbertenol* (**3**).—A solution of the phenol (**3**) (24 mg) in carbon tetrachloride (1 ml) was stirred

* The above m.p., mixed m.p., and spectral data coincided with those of dimethyl 4-methoxybenzene-1,3-dicarboxylate (**16**) (m.p. 97.5—98.5 °C, from hexane–chloroform) prepared from 2,4-dimethylanisole.

† The above m.p. and spectroscopic properties were coincident with those of methyl 2-methoxy-5-nitrobenzoate (**19**) (m.p. 101—102 °C, from chloroform) prepared by nitration of salicylic acid followed by treatment with diazomethane.

with bromine, in the same manner as described for the phenol (**2**), for 6 h. The usual work-up and purification by p.l.c. [hexane–ether (9:1)] gave the bromide (**21**) (28 mg) as crystals.

(−)-β-*Bromoherbertenol* [2-*bromo*-3-*hydroxyherbertene*] (**21**). M.p. 80—81 °C (from hexane); $[\alpha]_D$ −44.0° (*c* 0.9) (Found: C, 60.7; H, 7.2. $C_{15}H_{21}BrO$ requires C, 60.61; H, 7.12%); $\nu_{max.}$ 3 545, 1 605, 1 575, 1 480, 1 400, 1 380, 1 370, 1 360, 1 328, 1 310, 1 290, 1 240, 1 220, 1 114, 1 002, 830, and 725 cm^{-1}; δ_H 0.66, 1.06, 1.23, and 2.27 (each 3 H, s), 5.28 (1 H, s, exchangeable with D_2O), and 6.99 and 7.18 (each 1 H, d, *J* 2.0 Hz); *m/z* 298, 296 (M^+, 53, 51%), 283 (8), 281 (9), 241 (9), 239 (9), 228 (96), 226 (100), 213 (36), 211 (43), 201 (11), 199 (9), 174 (9), 160 (77), 146 (27), 135 (23), 115 (14), 103 (8), 91 (17), 77 (16), 69 (16), 55 (18), and 41 (27).

Transformation of (−)-3-*Bromoherbertene* (**10**) *into* (−)-β-*Herbertenol* (**3**).—Under dry nitrogen a solution (0.9 ml) of 1.6M-butyl-lithium in hexane and dry ether (1.5 ml) were stirred for 15 min at room temperature. To this solution was added a solution of the bromide (**10**) (78 mg) in dry ether (1.5 ml), and the mixture was stirred for a further 1 h. The solution was then cooled to −65 °C, and a solution of nitrobenzene (0.15 ml) in dry ether (1.5 ml) was added dropwise during 15 min. After the addition, the reaction was immediately quenched by addition of methanol (3 ml). The reaction mixture was stirred for 30 min and then diluted with ether.[31] The solution, after being acidified, was washed successively with water and saturated aqueous sodium chloride, and dried ($MgSO_4$). The solvent was evaporated off under reduced pressure to leave a crude product which was purified by p.l.c. [hexane–ethyl acetate (9:1)] to give the phenol (**3**) (18 mg), m.p. 80—80.5 °C (from hexane); $[\alpha]_D$ −69.9° (*c* 0.6) (Found: C, 82.55; H, 10.4%), along with the hydrocarbon (**1**) (26 mg). The physical constants and spectral data were in good agreement with those of the natural (−)-β-herbertenol (**3**).

Ozonolysis of (−)-β-*Herbertenol* (**3**).—The phenol (**3**) (34 mg) was dissolved in ethyl acetate (8 ml) and was ozonized for 8 h at −65 °C. The ozonide was treated in the manner described for that of α-herbertenol (**2**). The product, recovered in the usual way, was purified by p.l.c. [hexane–acetone (4:1)] to yield (−)-camphonanic acid (**12**) (8 mg), m.p. 189—190 °C (sealed tube, from hexane); $[\alpha]_D$ −18.0° (*c* 0.6). The spectroscopic properties (i.r., ^1H n.m.r., and m.s.) were identical with those of authentic (−)-camphonanic acid (**12**).

Demethylation of the Methoxy Aldehyde (**17**).—Under dry nitrogen a solution of the methyl ether (**17**) (24 mg) in methylene dichloride (1 ml) was added dropwise to a stirred solution of boron tribromide (0.1 ml) in methylene dichloride (0.5 ml) cooled to −70 °C. The reaction mixture was stirred for 4 h at −70 °C and then overnight at room temperature, water was added, and the mixture was stirred for 30 min at room temperature and then extracted with ether.[32] The usual work-up of the solution gave a crude product which was purified by p.l.c. [hexane–acetone (4:1)] to yield the hydroxy aldehyde (**4**) (18 mg), m.p. 133.5—134.5 °C (from hexane–chloroform); $[\alpha]_D$ −74.2° (*c* 0.8) (Found: C, 77.8; H, 9.0%). The i.r., ^1H n.m.r., and mass spectra were superposable on those of the natural product (**4**).

Acetylation of (−)-*Herbertenediol* (**5**).—The diol (**5**) (23 mg) was mixed with acetic anhydride (0.5 ml) and pyridine (0.3 ml), and the mixture was stirred for 3 h at room temperature. A crude product was obtained by the same manner as described for the phenols (**2**) and (**3**) and was purified by p.l.c. [hexane–ethyl acetate (4:1)] to give the diacetate (**22**) (32 mg) as a gum.

1,2-*Diacetoxyherbertene* (**22**). $[\alpha]_D$ −22.4° (*c* 1.0) (Found: C, 71.4; H, 8.3. $C_{19}H_{26}O_4$ requires C, 71.67; H, 8.23%); $\nu_{max.}$ 1 770, 1 610, 1 585, 1 363, 1 292, 1 205, 1 190, 1 135, 1 120, 1 025, 1 010, and 900 cm^{-1}; δ_H 0.75, 1.17, 1.25, 2.12, 2.18, and 2.33 (each 3 H, s) and 6.79 and 7.00 (each 1 H, d, *J* 2.0 Hz); *m/z* 318 (M^+, 31%), 276 (62), 246 (11), 234 (100), 216 (9), 206 (8), 193 (11), 178 (16), 164 (49), 152 (38), 151 (41), 135 (12), 121 (7), 105 (8), 91 (16), 77 (9), 69 (23), 55 (16), 43 (29), and 41 (18).

Oxidation of (−)-α-*Herbertenol* (**2**) *with Benzoyl Peroxide*.—Under nitrogen a solution of the phenol (**2**) (48 mg) and benzoyl peroxide (62 mg) in dry benzene (2 ml) was stirred and heated for 1 h at 90—100 °C.[20] The mixture was diluted with ether and treated by the usual way to afford a crude product which was purified by p.l.c. [hexane–ethyl acetate (9:1)] to yield a pair of the positional isomers of the hydroxy benzoate (**23a** and **b**) 34 mg) as a gum. The isomers 2-benzoyloxy-1-hydroxy- (**23a**) and 1-benzoyloxy-2-hydroxy-herbertene (**23b**); mixture (**23a** and **b**) had $\nu_{max.}$ 3 590, 3 430, 1 745, 1 715, 1 600, 1 485, 1 450, 1 385, 1 373, 1 362, 1 275, 1 215, 1 185, 1 065, 1 030, and 710 cm^{-1}; *m/z* 328 (M^+, 10%), 256 (3), 105 (100), 91 (2), 77 (18), 69 (3), 55 (2), and 41 (4); (**23a**) had δ_H 0.85, 1.13, 1.29, and 2.05 (each 3 H, s), 6.26 and 6.67 (each 1 H, br s), 7.1—7.7 (3 H, complex), and 7.9—8.4 (2 H, complex); (**23b**) had δ_H 0.77, 1.16, 1.40, and 2.26 (each 3 H, s), 6.81 and 6.95 (each 1 H, d, *J* 2.0 Hz), 7.1—7.7 (3 H, complex), and 7.9—8.4 (2 H, complex).

Benzoylation of the Hydroxy Benzoate Isomers (**23a** *and* **b**) *with Benzoyl Chloride*.—The positional isomers (**23a** and **b**) (21 mg) and benzoyl chloride (21 mg) were stirred in pyridine (0.5 ml) for 4 h at room temperature. The mixture was diluted with ether and the usual work-up gave a crude product. Purification by p.l.c. [hexane–ethyl acetate (50:1)] provided the dibenzoate (**24**) (25 mg) as crystals.

1,2-*Dibenzoyloxyherbertene* (**24**). M.p. 150—151 °C (from hexane); $[\alpha]_D$ −23.1° (*c* 1.1) (Found: C, 78.6; H, 6.9. $C_{29}H_{30}O_4$ requires C, 78.70; H, 6.83%); $\nu_{max.}$ 1 750, 1 603, 1 585, 1 390, 1 375, 1 365, 1 260, 1 240, 1 200, 1 185, 1 085, 1 065, 1 030, and 710 cm^{-1}; δ_H 0.89, 1.16, 1.31, and 2.42 (each 3 H, s), 6.9—7.5 (8 H, complex), and 7.7—8.1 (4 H, complex); *m/z* 442 (M^+, 6%), 360 (2), 336 (6), 320 (5), 264 (5), 255 (11), 215 (3), 187 (7), 174 (3), 105 (100), 91 (2), 77 (6), and 41 (2).

Reduction of the Dibenzoate (**24**) *with Lithium Aluminium Hydride*.—A suspension of lithium aluminium hydride (9 mg) in dry ether (0.4 ml) was added to a stirred solution of the dibenzoate (**24**) (43 mg) in dry ether (1 ml). After being stirred for 3 h in an ice-bath, the reaction mixture was poured into cold 5% aqueous hydrochloric acid and extracted with ether. Usual work-up gave a product which was purified by p.l.c. [hexane–ethyl acetate (9:1)] to yield the diol (**5**) (17 mg), m.p. 91—92 °C (from hexane); $[\alpha]_D$ −51.1° (*c* 0.9) (Found: C, 76.6; H, 9.8%). The spectral data (i.r., ^1H n.m.r., and m.s.) were coincident with those of the natural (−)-herbertenediol (**5**).

Reduction of the Hydroxy Benzoate Isomers (**23a** *and* **b**) *with Lithium Aluminium Hydride*.—To a stirred solution of the isomers (**23a** and **b**) (35 mg) in dry ether (2 ml), cooled in an ice-bath, was added a suspension of lithium aluminium hydride (8 mg) in dry ether (0.5 ml) and the mixture was stirred for a further 3 h. The reaction mixture was treated by the same manner as described for the reduction of the dibenzoate (**24**). Recovery of the product in the usual manner gave a gum which was purified by p.l.c. [hexane–ethyl acetate (4:1)] to afford the diol (**5**) (21 mg). The i.r. and ^1H n.m.r. spectra were identical with those of the natural product (**5**).

Reduction of (−)-*Herbertenolide* (**6**) *with Lithium Aluminium Hydride*.—A mixed solution of the lactone (**6**) (32 mg) in dry ether (1 ml) and lithium aluminium hydride (8 mg) in dry ether

(0.5 ml) was stirred for 2 h in an ice-bath. To the solution was added 5% aqueous sodium hydroxide and the mixture was stirred for 1 h, then filtered, and the filtrate was extracted with ether. The usual work-up afforded a product which was purified by p.l.c. [chloroform–ethyl acetate (9:1)] to yield the hydroxy phenol (**25**) (23 mg) as crystals.

1,14-*Dihydroxyherbertene* (**25**).—M.p. 139.5—140.5 °C (from hexane–ethyl acetate); $[\alpha]_D$ −88.1° (*c* 0.8) (Found: C, 77.0; H, 9.6. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%); $\nu_{max.}$ 3 500—2 500, 1 610, 1 508, 1 493, 1 410, 1 375, 1 230, 1 050, and 1 030 cm^{-1}; δ_H 0.80, 1.47, and 2.24 (each 3 H, s), 3.30 and 4.02 (each 1 H, d, *J* 11.5 Hz), 6.64 (1 H, d, *J* 8.0 Hz), 6.81 (1 H, dd, *J* 8.0 and 2.0 Hz), and 7.05 (1 H, d, *J* 2.0 Hz); *m/z* 234 (M^+, 31%), 216 (14), 201 (28), 187 (4), 173 (13), 161 (28), 148 (36), 135 (100), 121 (24), 105 (12), 91 (13), 77 (12), 69 (7), 55 (10), and 41 (16).

Methylation of the Hydroxyphenol (**25**).—A solution of the phenol (**25**) (33 mg) in acetone (3 ml) was mixed with methyl iodide (46 mg) and potassium carbonate (21 mg), and the mixture was heated under reflux for 6.5 h, and diluted with ether. The usual work-up gave a crude product which was purified by p.l.c. [hexane–ethyl acetate (4:1)] to yield the methyl ether (**26**) (32 mg) as a gum.

14-*Hydroxy*-1-*methoxyherbertene* (**26**). $[\alpha]_D$ −78.9° (*c* 1.5) (Found: C, 77.1; H, 10.0. $C_{16}H_{24}O_2$ requires C, 77.37; H, 9.74%); $\nu_{max.}$ 3 650, 3 510, 1 602, 1 580, 1 493, 1 462, 1 370, 1 240, 1 230, 1 180, 1 160, 1 080, 1 055, 1 030, and 973 cm^{-1}; δ_H 0.64, 1.35, 2.27, and 3.78 (each 3 H, s), 3.40 and 3.76 (each 1 H, d, *J* 11.5 Hz), 6.65 (1 H, d, *J* 8.0 Hz), 6.87 (1 H, dd, *J* 8.0 and 2.0 Hz), and 7.03 (1 H, d, *J* 2.0 Hz); *m/z* 248 (M^+, 50%), 215 (2), 201 (1), 187 (2), 175 (27), 162 (28), 149 (100), 135 (18), 119 (13), 105 (13), 91 (13), 77 (8), 69 (6), 55 (8), and 41 (12).

Formation of the Cyclic Ether (**27**) *from the Hydroxyphenol* (**25**).—(*a*) Triphenyl phosphite methiodide (97 mg), which was prepared from triphenyl phosphite and methyl iodide by the method of Verheyden and Moffatt,[21] was added to a solution of the hydroxyphenol (**25**) (20 mg) in HMPA (0.4 ml) and the mixture was stirred for 3.5 h at room temperature. Sodium cyanoborohydride (26 mg) was added to the reaction mixture which was then stirred for 1.5 h at 70 °C.[22] The mixture was diluted with ether and washed with water. The usual work-up gave a product which was purified by p.l.c. (hexane) to yield the cyclic ether (**27**) (7 mg) as a gum.

(*b*) A solution of the diol (**25**) (10 mg) in HMPA (0.4 ml) was stirred with triphenyl phosphite methiodide (41 mg) for 4.5 h at room temperature.[21] The reaction mixture was diluted with ether, and the solution was washed successively with 5% aqueous sodium thiosulphate, water, saturated aqueous sodium chloride, and water. The usual work-up and p.l.c. [hexane–ethyl acetate (9:1)] gave the ether (**27**) (8 mg).

(*c*) The diol (**25**) (21 mg) and PTSA (1 mg) were heated under reflux in benzene (1 ml) for 5 h, and then diluted with ether. The usual work-up afforded a product which was purified by p.l.c. [hexane–ethyl acetate (25:1)] to yield the cyclic ether (**27**) (9 mg).

1,14-*Epoxyherbertene* (**27**). Gum; $[\alpha]_D$ −32.8° (*c* 0.7) (Found: C, 83.3; H, 9.6. $C_{15}H_{20}O$ requires C, 83.28; H, 9.32%); $\nu_{max.}$ 1 492, 1 382, 1 372, 1 257, 1 235, 1 210, 1 180, 1 142, 1 005, and 971 cm^{-1}; δ_H 0.77, 1.06, and 2.22 (each 3 H, s), 3.96 and 4.32 (each 1 H, d, *J* 10.0 Hz), 6.53 (1 H, d, *J* 8.0 Hz), 6.62 (1 H, d, *J* 2.0 Hz), and 6.76 (1 H, dd, *J* 8.0 and 2.0 Hz); *m/z* 216 (M^+, 58%), 201 (100), 185 (2), 173 (8), 169 (21), 145 (51), 131 (12), 121 (17), 115 (9), 105 (16), 91 (13), 77 (12), 69 (8), 55 (11), and 41 (19).

Formation of the Cyclic Ether (**27**) *from the Methyl Ether* (**26**).—A solution of the methyl ether (**26**) (27 mg) in HMPA (1 ml) was stirred with triphenyl phosphite methiodide (150 mg) for 3.5 h at room temperature and sodium cyanoborohydride (37 mg) was then added to the mixture. After the mixture had been heated and stirred for 1.5 h at 70 °C, the reaction product was treated in the same manner as in the case of cyclization of the diol (**25**), and the cyclic ether (**27**) (9 mg) was obtained.

Ether Cleavage of the Cyclic Ether (**27**).—To a cooled solution of the ether (**27**) (15 mg) in ethanethiol (0.5 ml) was added aluminium trichloride (58 mg), and the mixture was stirred for 6 h in an ice-bath and then diluted with ether.[23] The solution was washed successively with 5% hydrochloric acid and water, dried ($MgSO_4$), and concentrated under reduced pressure. The sulphide (**28**) (17 mg) was isolated by p.l.c. [hexane–ethyl acetate (25:1)] from the reaction mixture.

14-*Ethylthio*-1-*hydroxyherbertene* (**28**). Gum; $[\alpha]_D$ +11.5° (*c* 0.9); $\nu_{max.}$ 3 525, 3 300, 1 605, 1 500, 1 370, 1 280, 1 250, 1 170, 1 140, and 1 083 cm^{-1}; δ_H 0.79, 1.40, and 2.23 (each 3 H, s), 1.26 (3 H, t, *J* 7.5 Hz), 2.52 (2 H, q, *J* 7.5 Hz), 2.76 and 3.21 (each 1 H, d, *J* 12.0 Hz), 5.42 (1 H, br s, exchangeable with D_2O), 6.43 (1 H, d, *J* 8.0 Hz), 6.72 (1 H, dd, *J* 8.0 and 2.0 Hz), and 6.96 (1 H, d, *J* 2.0 Hz); *m/z* 278 (M^+, 13%), 232 (6), 216 (20), 201 (6), 168 (11), 161 (55), 148 (15), 135 (100), 121 (45), 105 (8), 91 (9), 77 (7), 69 (8), 55 (7), and 41 (14).

Hydrogenolysis of the Sulphide (**28**) *with Raney Nickel*.—A solution of the sulphide (**28**) (17 mg) and W-4 Raney nickel (250 mg) in ethanol (5 ml) was heated under reflux for 1.5 h.[33] After the mixture had cooled, the catalyst was filtered off and washed with ether. The filtrate was concentrated and submitted to p.l.c. [hexane–ethyl acetate (9:1)] to yield the phenol (**2**) (12 mg), $[\alpha]_D$ −66.7° (*c* 0.4). The spectral data (i.r., ^1H n.m.r., and m.s.) were identical with those of natural (—)-α-herbertenol (**2**).

Test of Antifungal Activity.—The growth inhibitory effect of the sesquiterpenoids (−)-α-herbertenol (**2**), (−)-β-herbertenol (**3**), (−)-α-formylherbertenol (**4**), and (−)-β-bromoherbertenol (**21**) on the plant pathogenic fungi, *Botrytis cinerea*, *Rhizoctonia solani*, and *Pythium debaryanum*, was tested by the following method. A mycelial disc (5 mm in diameter) of each of the pathogenic fungi was placed on potato–sucrose–agar medium with or without each of the test compounds, and cultured for 5 days at 25 °C. The inhibition percentage was obtained by measuring the diameter of the mycelial colony. Results are shown in Table 3.

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