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THREE NEW SESQUITERPENE PHENOLS OF THE *ENT*-HERBERTANE CLASS FROM THE LIVERWORT *HERBERTA ADUNCA*

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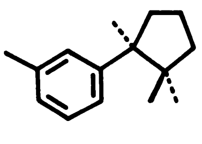
Three sesquiterpene phenols with an *ent*-herbertane skeleton have been isolated from the liverwort *Herberta adunca*, and the elucidation of their structures and absolute configurations has been achieved on the basis of the chemical and spectral evidence.

In a previous paper, we reported the isolation and structural determination of an aromatic sesquiterpene hydrocarbon, (-)-herbertene (1), with a novel carbon skeleton from the liverwort *Herberta adunca* (Dicks.) S. Gray belonging to the Herbertaceae.[1] From the same liverwort we now isolated three new sesquiterpene phenols named (-)-α-herbertenol (2), (-)-α-formylherbertenol (3), and (-)-β-herbertenol (4) which had the novel *ent*-herbertane skeleton, differing in the substituent pattern on the six membered ring from the known *ent*-cuparane skeleton such as (-)-cuparene (5) and (-)-δ-cuparenol (6) isolated from another liverwort *Bazzania pompeana*.[2] On the basis of the following chemical and spectral evidence the structures and absolute configurations were, respectively, elucidated to be 1S-(2′-hydroxy-5′-methylphenyl)-1,2,2-trimethylcyclopentane (2), 1S-(5′-formyl-2′-hydroxyphenyl)-1,2,2-trimethylcyclopentane (3), and 1S-(4′-hydroxy-3′-methylphenyl)-1,2,2-trimethylcyclopentane (4).



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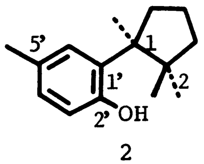

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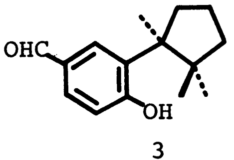

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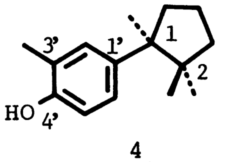

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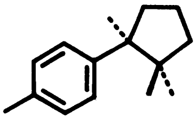

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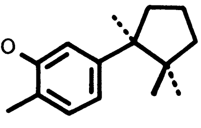

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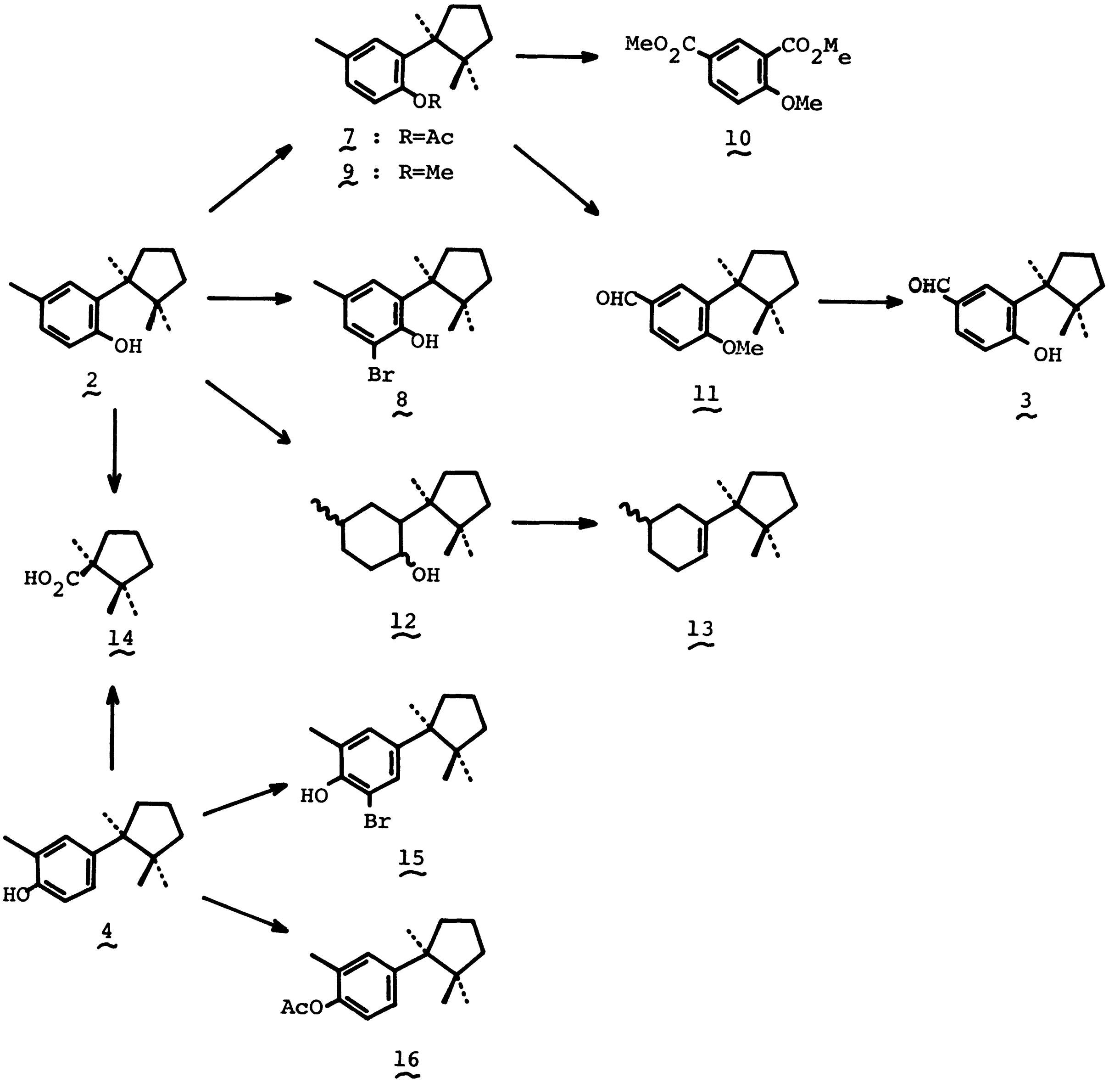
The three sesquiterpene phenols, (2): $C_{15}H_{22}O$; oil; 3,5-DNB mp 143-144 °C; $[\alpha]_D$ -55°, (3): $C_{15}H_{20}O_2$; mp 134-135 °C; $[\alpha]_D$ -66°, and (4): $C_{15}H_{22}O$; mp 77-78 °C; $[\alpha]_D$ -47°, were isolated from the methanol extract in yields of 6.5, 0.1, and 0.5 %, respectively, by a combination of column chromatography and preparative TLC.[3]

The spectral properties of the major compound (2) revealed that it was a bicyclic sesquiterpenoid, consisting of a 2,4-disubstituted phenol [λ 283 and 289 nm(ε 2540 and 2300); ν 3640, 3605, 3530, 1610, and 1500 cm^{-1}; δ 4.57(1H, s: exchangeable with D_2O), 6.35(1H, d, J=8.0), 6.70(1H, dd, J=8.0 and 2.0), and 6.95 (1H, d, J=2.0); δ_C 116.9(d), 127.3(d), 128.9(s), 130.0(d), 133.2(s), and 152.3(s)], the two substituent groups of which were a methyl [δ 2.25(3H, s); δ_C 20.9(q)] and a cyclopentane ring with three tertiary methyls [ν 1385, 1370, and 1360 cm^{-1}; δ 0.75, 1.18, and 1.38(each 3H, 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)].[4)] The sesquiterpene phenol (2), which produced an acetate (7), $C_{17}H_{24}O_2$; $[\alpha]_D$ -38°; ν 1750 cm^{-1}; δ 2.17(3H, s), was treated with Br_2 to give a bromide (8), $C_{15}H_{21}OBr$; $[\alpha]_D$ -56°. The ^1H-NMR spectrum showed only two aromatic proton signals as a pair of doublets, δ 7.00(d, J=2.0) and 7.10(d, J=2.0), performing *meta* coupling to each other. The 1,2,4-trisubstituted pattern of the original benzene nucleus was finally confirmed as the 2,4-disubstituted phenol by the following chemical reactions: the phenol (2), after conversion to a methyl ether (9), $C_{16}H_{24}O$; $[\alpha]_D$ -56°; δ 3.74(3H, s), was oxidized with dilute HNO_3 in a sealed tube followed by treatment with CH_2N_2 to produce dimethyl 4-methoxybenzene-1,3-dicarboxylate (10), $C_{11}H_{12}O_5$; mp 96.5-97.5 °C [lit. mp 95-96 °C].[5)] The identification was also certified by coincidence of the spectral data with those of the authentic sample prepared from 2,4-dimethylphenol.

In order to select the position of the hydroxy group from the two possibilities, the methyl ether (9) was exchanged to a formyl compound (11), $C_{16}H_{22}O_2$; $[\alpha]_D$ -64°; ν 1700 cm^{-1}; δ 9.78(1H, s), by oxidation with MnO_2. The two aromatic protons, δ 7.58(dd, J=8.0 and 2.0) and 7.78(d, J=2.0), with mutual *meta* coupling among themselves suffered an anisotropic deshielding effect of the neighboring formyl group to a larger downfield shift comparing with those, δ 6.81(dd, J=8.0 and 2.0) and 6.99(d, J=2.0), of the parent compound (9). Now, the spectra of the aldehyde (11) was close to those of the natural formyl compound (3) and the ether (11) was treated with BBr_3 to revert to a phenol (3), $C_{15}H_{20}O_2$; mp 133.5-134.5 °C; $[\alpha]_D$ -74°, whose spectral data as well as the optical rotation were all consistent with those of the natural product [ν 3620, 3320, 1700, 1675, 1595, and 1585 cm^{-1}; δ 0.75, 1.22, and 1.43(each 3H, s), 6.97(1H, d, J=8.0), 7.58(1H, d, J=8.0 and 2.0), 7.85(1H, d, J=2.0), 8.40(1H, s: exchangeable with D_2O), and 9.76(1H, s)]. Alternatively, the sesquiterpene hydrocarbon (13), $C_{15}H_{26}$, which was prepared from a configurational mixture of sesquiterpene alcohol (12), $C_{15}H_{28}O$, obtained by hydrogenation of the phenol (2) afforded no signals of vinyl methyls on the ^1H-NMR spectrum but the signal due to a vinyl proton at δ 5.43(1H, t, J=3.0). For confirmation of the cyclopentyl moiety the phenol (2) was ozonolyzed to an acid (14), $C_9H_{16}O_2$; mp 189-190 °C; $[\alpha]_D$ -13° [lit. mp 191-192 °C; $[\alpha]_D$ +21°,[6)] which was identified as (-)-camphonanic acid by coincidence of the spectral data and optical rotation with those of the authentic compound produced from (-)-*ent*-cuparene (5).[2)]

Accordingly, the structure including the absolute configuration of (-)-α-herbertenol is represented by 1S-(2'-hydroxy-5'-methylphenyl)-1,2,2-trimethylcyclopentane (2) and (-)-α-formylherbertenol is 1S-(5'-formyl-2'-hydroxyphenyl)-1,2,2-trimethylcyclopentane (3).



Next, the third phenol (4) had the spectral figures similar to those of the major herbertenol (2) and of δ-cuparenol (6). The properties suggested it was a sesquiterpene phenol substituted with both the methyl and the 1,2,2-trimethylcyclopentyl group [λ 277 and 284 nm(ε 1500 and 1380); ν 3615, 3430, 1610, 1600, 1505, 1385, 1375, and 1365 cm^{-1}; δ 0.55, 1.03, 1.22, and 2.18(each 3H, s), 4.48 (1H, s: exchangeable with D_2O), 6.43(1H, d, J=8.0), 6.87(1H, dd, J=8.0 and 2.0), and 6.97(1H, d, J=2.0)]. The stereostructure of the cyclopentyl part was certified by formation of (−)-camphonanic acid (14), $C_9H_{16}O_2$; mp 188.5-189.5 °C; $[\alpha]_D$ −18°, by ozonolysis of the compound (4). On the benzene ring the aromatic protons appeared as three signals of the *ortho*, *ortho-meta*, and *meta* couplings, suggesting the 1,2,4-trisubstituted benzene nucleus. Furthermore, its bromide (15), $C_{15}H_{21}OBr$; mp 80-81 °C; $[\alpha]_D$ −44°, gave two aromatic protons showing *meta* coupling to each other at δ 6.99(d, J=2.0) and 7.19(d, J=2.0). Therefore, the minor phenol (4) should be consisted of the herbertane skeleton and be a positional isomer of the major (2), having the hydroxy group at the *ortho* position of the aromatic methyl, the chemical shift, δ 2.18, of which appeared at upper field than that, δ 2.25, of α-herbertenol (2). The *ortho* relationship of the hydroxy group and the aromatic methyl was also explained by comparing chemical shift values of the aromatic methyls between the phenol (4) and its acetate (16), $C_{17}H_{24}O_2$; $[\alpha]_D$ -51°; ν 1760 cm^{-1}; δ 2.25(3H, s), with those between the related phenols and their acetates on ^1H-NMR spectra as shown in Table: in all compounds examined the methyl signals of *ortho* position to the hydroxy groups were shifted to upfield by anisotropic shielding effect of the formed acetoxy group, in contrast with the *meta* and *para* methyls undergone a deshielding effect. These results were supported by LIS experiment of the both phenols, the ΔEu values of α-herbertenol (2) and β-herbertenol (4) were 0.6 and 5.1, respectively.

Table. Difference of chemical shifts of the aromatic methyls between the phenols and their acetate derivatives

phenols	chemical shifts of the aromatic methyls		
	R-OH	R-OAc	(R-OH)-(R-OAc)
α-herbertenol (2)	2.25	2.30	-0.05
β-herbertenol (4)	2.18	2.15	+0.03
δ-cuparenol (6)	2.12	2.07	+0.05
ortho-cresol	2.16	2.10	+0.06
meta-cresol	2.16	2.32	-0.16
para-cresol	2.26	2.31	-0.05

(in CCl_4 solution)

These novel enantiomeric structures formed by 1,2-methyl migration of *ent*-cuparane skeleton agree with our result that the liverworts generally metabolite the enantiomeric sesquiterpenoids corresponding to antipodes for the normal stereostructures produced by higher plants,⁷⁾ and they are valuable as the diagnoses in chemosystematic of the liverworts.

References

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3) Satisfactory analyses of the natural products were obtained, and the optical rotations were measured in $CHCl_3$ solution.

4) IR and ^1H-NMR spectra were determined in CCl_4 solution, and UV and ^{13}C-NMR in EtOH and $CDCl_3$ solutions, respectively. All new compounds gave spectra in good accord with the assigned structures.

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