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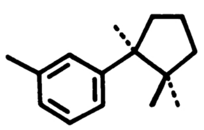
THREE NEW SESQUITERPENE PHENOLS OF THE *ENT*-HERBERTANE CLASS FROM THE LIVERWORT *HERBERTA ADUNCA*

Akihiko MATSUO,* Shunji YUKI, Mitsuru NAKAYAMA,
and Shûichi HAYASHI+
Department of Chemistry, Faculty of Science, Hiroshima
University, Higashisenda-machi, Naka-ku, Hiroshima 730
+Department of Chemistry, Faculty of Science, Okayama
University of Science, Ridai-cho, Okayama 700

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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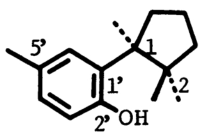

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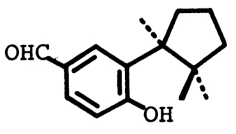

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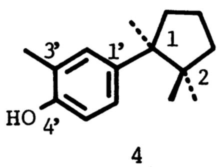

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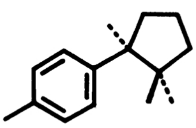
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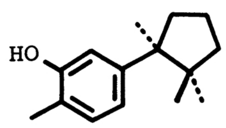

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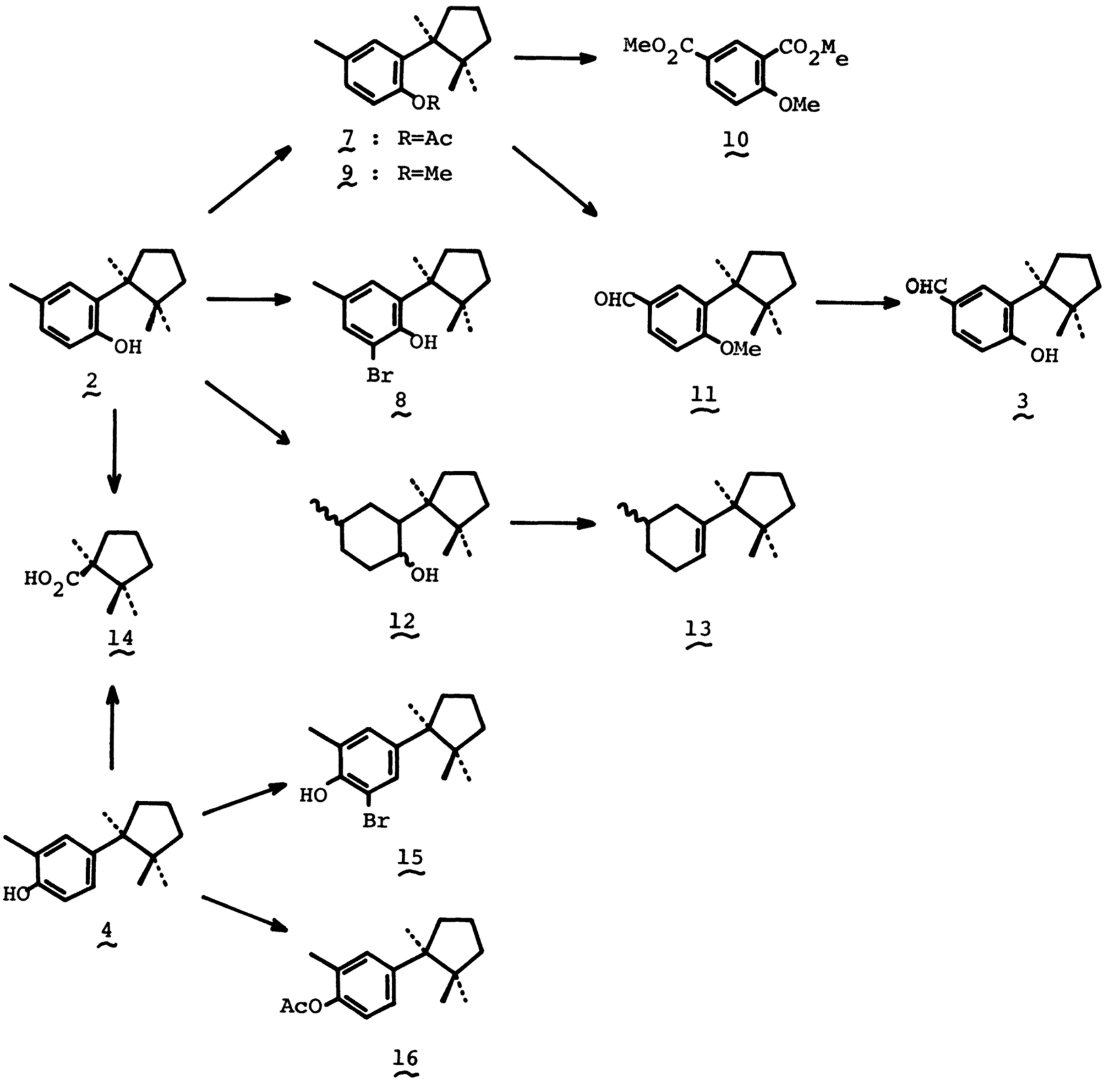
The three sesquiterpene phenols, (2): $C_{15}H_{22}O$; oil; 3,5-DNB mp 143-144 °C; $[\alpha]_D$ -55°, (3): $C_{15}H_{20}O_2$; mp 134-135 °C; $[\alpha]_D$ -66°, and (4): $C_{15}H_{22}O$; mp 77-78 °C; $[\alpha]_D$ -47°, were isolated from the methanol extract in yields of 6.5, 0.1, and 0.5 %, respectively, 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 ^{1}H-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 ^{1}H-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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