

89)

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

REPRINTED FROM

CHEMISTRY
LETTERS

The Chemical Society of Japan

1982

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

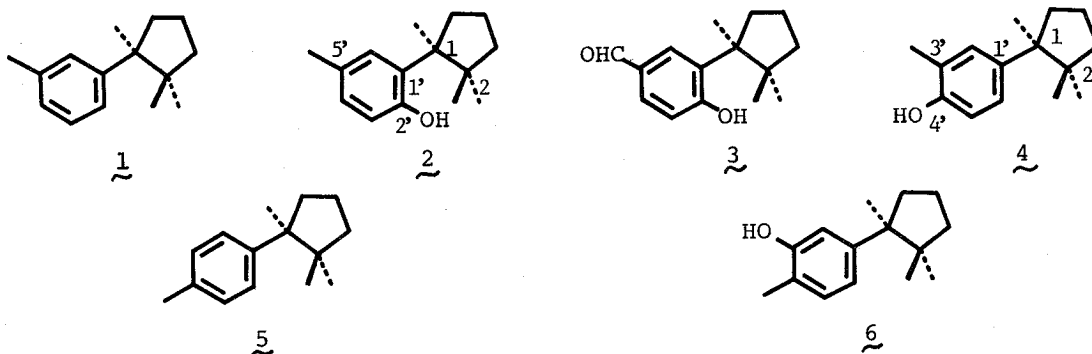
Akihiko MATSUO,^{*} Shunji YUKI, Mitsuru NAKAYAMA,
and Shûichi HAYASHI[†]

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).

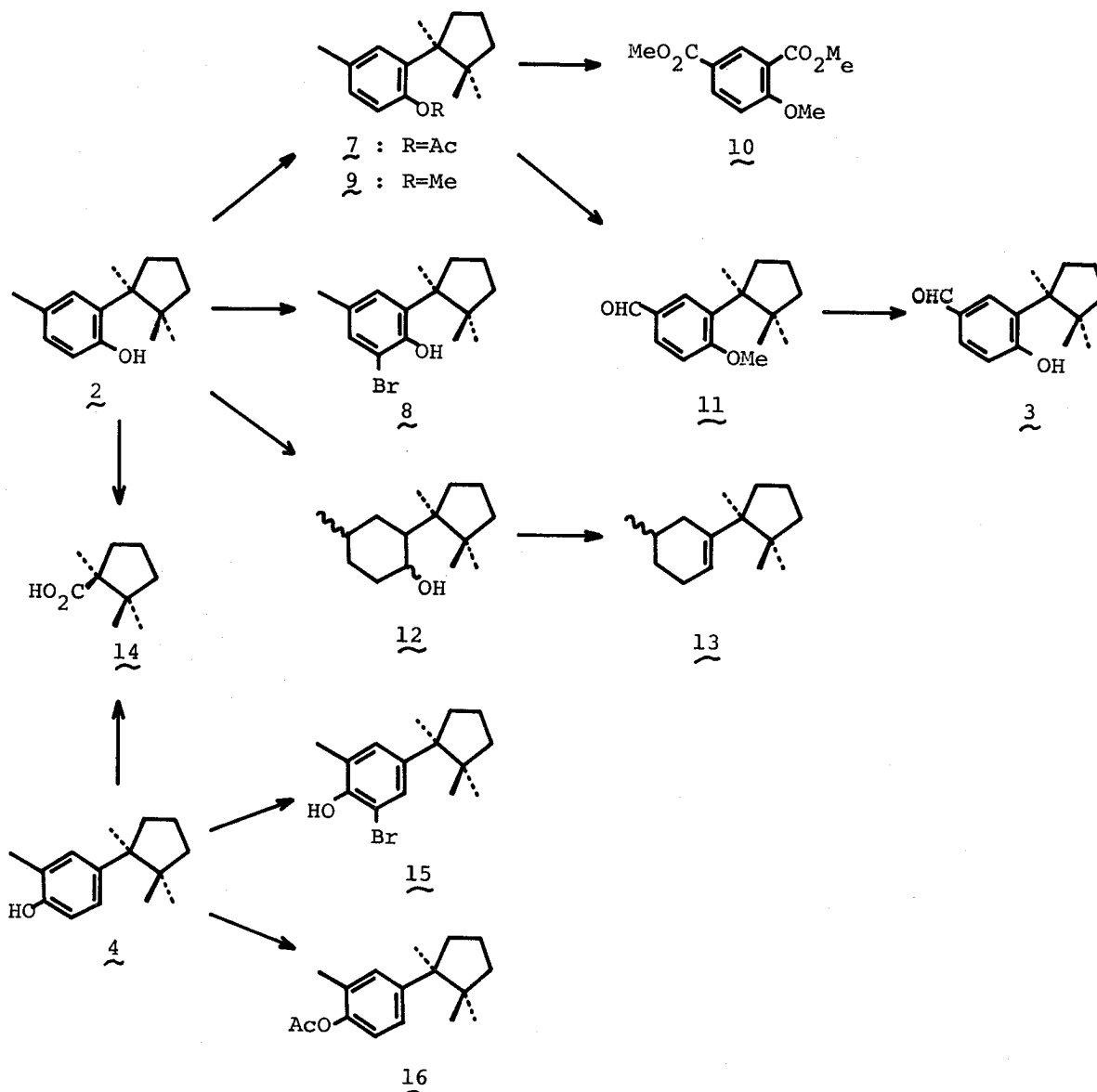


The three sesquiterpene phenols, (2): $C_{15}H_{22}O$; oil; 3,5-DNB mp 143-144 °C; $[\alpha]_D -55^\circ$, (3): $C_{15}H_{20}O_2$; mp 134-135 °C; $[\alpha]_D -66^\circ$, and (4): $C_{15}H_{22}O$; mp 77-78 °C; $[\alpha]_D -47^\circ$, were isolated from the methanol extract in yields of 6.5, 0.1, and 0.5 %, 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), $\text{C}_{17}\text{H}_{24}\text{O}_2$; [α]_D -38° ; ν 1750 cm^{-1} ; δ 2.17(3H, s), was treated with Br_2 to give a bromide (8), $\text{C}_{15}\text{H}_{21}\text{OBr}$; [α]_D -56° . The $^1\text{H-NMR}$ 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), $\text{C}_{16}\text{H}_{24}\text{O}$; [α]_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), $\text{C}_{11}\text{H}_{12}\text{O}_5$; mp 96.5-97.5 $^\circ\text{C}$ [lit. mp 95-96 $^\circ\text{C}$].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), $\text{C}_{16}\text{H}_{22}\text{O}_2$; [α]_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), $\text{C}_{15}\text{H}_{20}\text{O}_2$; mp 133.5-134.5 $^\circ\text{C}$; [α]_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), $\text{C}_{15}\text{H}_{26}$, which was prepared from a configurational mixture of sesquiterpene alcohol (12), $\text{C}_{15}\text{H}_{28}\text{O}$, obtained by hydrogenation of the phenol (2) afforded no signals of vinyl methyls on the $^1\text{H-NMR}$ 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), $\text{C}_9\text{H}_{16}\text{O}_2$; mp 189-190 $^\circ\text{C}$; [α]_D -13° [lit. mp 191-192 $^\circ\text{C}$; [α]_D $+21^\circ$],⁶ which was identified as (-)-camphononic 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 herbertylene (2) and of δ -cuparene (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 (-)-camphonic acid (14), $\text{C}_9\text{H}_{16}\text{O}_2$; mp 188.5-189.5 $^\circ\text{C}$; $[\alpha]_{\text{D}}$ -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), $\text{C}_{15}\text{H}_{21}\text{OBr}$; mp 80-81 $^\circ\text{C}$; $[\alpha]_{\text{D}}$ -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 herbertylene 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), $C_{17}H_{24}O_2$; $[\alpha]_D -51^\circ$; 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 ΔE_u 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
<i>ortho</i> -cresol	2.16	2.10	+0.06
<i>meta</i> -cresol	2.16	2.32	-0.16
<i>para</i> -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

- 1) A. Matsuo, S. Yuki, M. Nakayama, and S. Hayashi, J. Chem. Soc., Chem. Commun., 1981, 864.
- 2) A. Matsuo, M. Nakayama, T. Maeda, Y. Noda, and S. Hayashi, Phytochemistry, 14, 1037 (1975).
- 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.
- 5) H. O. House and C. B. Hudson, J. Org. Chem., 35, 647 (1970).
- 6) C. Enzell and H. Erdtman, Tetrahedron, 4, 361 (1958).
- 7) a) S. Hayashi and A. Matsuo, Chemistry (Kyoto), 31, 518 (1976) and references therein; b) A. Matsuo, S. Sato, M. Nakayama, and S. Hayashi, J. Chem. Soc., Perkin Trans. 1, 1979, 2652 and references therein; c) A. Matsuo, K. Atsumi, M. Nakayama, and S. Hayashi, ibid., 1981, 2816 and references therein.

(Received February 4, 1982)