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ENANTIOMERIC CUPARENE-TYPE SESQUITERPENOIDS FROM *BAZZANIA POMPEANA**

A. MATSUO, M. NAKAYAMA, T. MAEDA, Y. NODA and S. HAYASHI

Department of Chemistry, Faculty of Science, Hiroshima University, Hiroshima 730, Japan

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Key Word Index—*Bazzania pompeana*; Hepaticae; liverwort; sesquiterpenoids; structural determination; (R)-(−)-cuparene; (R)-(−)-δ-cuparenol.

Abstract—Two enantiomeric cuparene-type sesquiterpenoids, (R)-(−)-cuparene (**1**) and (R)-(−)-δ-cuparenol (**2**), have been isolated from the liverwort, *Bazzania pompeana*. The structures and absolute configurations of the two compounds have been determined.

INTRODUCTION

The liverworts (*Hepaticae*), placed in a unique group of the plant kingdom, contain characteristic oil bodies in each cell of the haploid plant bodies (gametophytes) growing from the spores. In our investigations on the constituents of liverworts, several enantiomeric sesquiterpenoids, (−)-longiborneol, (−)-longifolene, (+)-α-himachalene, (−)-α-longipinene, (−)-maalioxide and (+)-cyclocolorenone [1, 2], have been isolated together with some new sesquiterpenoids [3–6]. These compounds are optical antipodes of sesquiterpenoids found in plants of a higher evolutionary level.

(R)-(−)-Cuparene (**1**), which is an optical antipode of the compound isolated from higher plants, and (R)-(−)-δ-cuparenol (**2**), which was a new cuparene-type sesquiterpene phenol with (R)-chirality, have been isolated from the essential oil of *Bazzania pompeana* (Lac.) Mitt. belonging to the *Lepidoziaceae* (*Hepaticae*). The present paper deals with the chemical proof on the stereostructural determination of these compounds.

RESULTS AND DISCUSSION

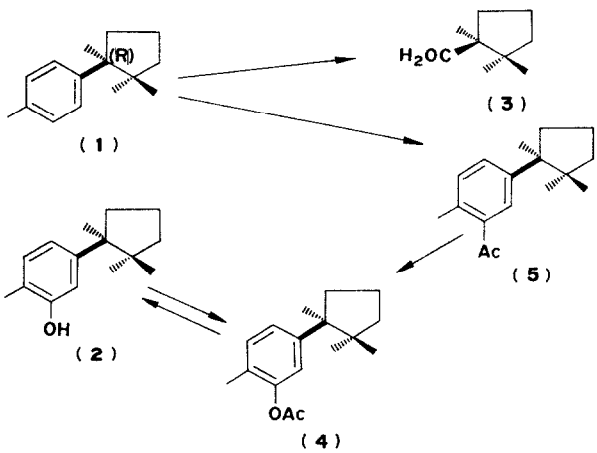
(R)-(−)-*Cuparene* (**1**). A hydrocarbon, $C_{15}H_{22}$, was isolated by means of fractional distillation followed by preparative GLC together with bazzanene and α-pompene previously reported [3–6]. The IR and PMR spectra indicated a *p*-methyl benzene nucleus (*ν* 1517, 812 cm^{-1}; *δ* 2·31, 3H, *s*; 6·95, 2H, *d*, *J* 8·5 Hz; 7·12, 2H, *d*, *J* 8·5 Hz), a *gem*-dimethyl (*ν* 1380, 1375, 1365; *δ* 0·57, 1·26, each 3H, *s*), a quarternary methyl (*δ* 1·06, 3H, *s*) and three aliphatic methylenes (*δ* 1·50–1·80, 6H, br *s*). The MS and UV spectra (see Experimental), as well as both the above spectra, were identical with those of (+)-cuparene, which had been isolated from *Chamaecyparis thyoides* and whose absolute configuration has been determined as S-chirality by Enzell *et al.* [7]. The optical rotation $[\alpha]_D$ −27·6° of the hydrocarbon, however, had an opposite sign to that $[\alpha]_D$ +65° of (+)-cuparene, even though the absolute value of the rotation was slightly smaller. Furthermore, ozonolysis of the hydrocarbon afforded (S)-(−)-camphonanic acid (**3**), which is known to be the optical antipode of (R)-(+)-camphonanic acid derived from the ozonolysis of (+)-cuparene [7]. Thus, the hydrocarbon is (R)-(−)-cuparene (**1**).

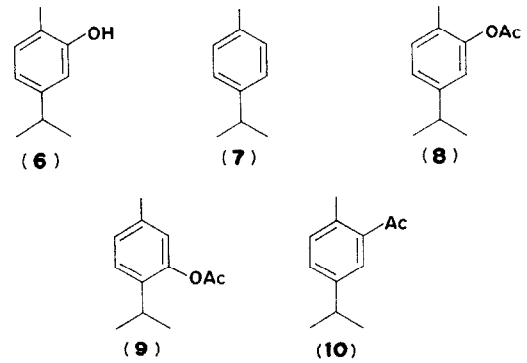
(R)-(−)-*δ-Cuparenol* (**2**) [8]. From a high boiling fraction of the essential oil of *B. pompeana* a new sesquiterpene phenol, $C_{15}H_{22}O$, was isolated as a minor colorless oily substance by repeated chromatography together with bazzanenol [5] and it was named δ-cuparenol in relation to α-, β- and γ-cuparenols [9]. The com-

* Part XX in the series "Chemical Constituents of Hepaticae". For Part XIX see Matsuo, A., Sato, S., Nakayama, M. and Hayashi, S. (1974) *Tetrahedron Letters* 3681.

pound afforded a crystalline 3,5-dinitrobenzoate and gave an oily mono-acetate (**4**), $C_{17}H_{24}O_2$. The IR and UV spectra suggested that the compound was a 2,5-disubstituted phenol [10]. The PMR spectrum also indicated the presence of a phenolic hydroxy group (δ 5·35, 1H, exchangeable with D_2O), an aromatic methyl (δ 2·12, 3H, *s*), three aromatic protons (δ 6·55–6·95, 3H, complex), three aliphatic methylenes (δ 1·58, 6H, br *s*) and three quaternary methyls (δ 0·53, 1·00, 1·17, each 3H, *s*). Although the PMR spectrum, except the signals of the phenolic hydroxy and aromatic protons, was similar to that of (R)-(−)-cuparene (**1**), the signal of the three aromatic protons resembled closely that of carvacrol (**6**) and a further signal (δ 0·53) of the three quaternary methyls showed an upfield shift possibly due to the anisotropic effect of the aromatic nucleus. The chemical and spectral evidence suggested that the structure of the compound was a hydroxy derivative of cuparene.

Information on the exact position of the hydroxy group was obtained from the chemical shift of the aromatic methyl in (−)-δ-cuparenyl acetate





(**4**) and comparison with that of the aromatic methyl group in (−)-cuparene (**1**) showing a marked upfield shift (0·24 ppm in CCl_4) attributable to the anisotropic effect of the acetyl group. Furthermore, when the chemical shift and the solvent effect of the aromatic methyl group were compared between (−)-δ-cuparenyl acetate (**4**), (−)-cuparene (**1**), carvacryl acetate (**8**), thymyl acetate (**9**) and *p*-cymene (**7**) (see Table 1), the shift (δ 2·08) of (−)-δ-cuparenyl acetate was the same as that of carvacryl acetate and both (−)-δ-cuparenyl acetate and carvacryl acetate showed a similar solvent effect. Therefore, the relation between (−)-δ-cuparenyl acetate and (−)-cuparene is similar to that between carvacryl acetate and *p*-cymene. Accordingly, (−)-δ-cuparenol isolated from *B. pompeana* is (−)-2-hydroxy cuparene, whose structure was also supported by MS which showed the characteristic ions

$C_9H_{12}O$ ([ ]$^+$·,

base peak, *m/e* 136·0892) and

$C_{10}H_{12}O$ ([ ]$^+$·

rel. intensity 82% *m/e* 148·0900).

Table 1. Chemical shifts of aromatic methyls of (R)-(−)-δ-cuparenyl acetate (**4**) and related compounds (δ_{ppm})

Compounds	Chemical shifts of aromatic methyls CCl_4	C_6D_6	Δ Value*
(R)-(−)-δ-Cuparenyl acetate (**4**)	2·07	2·04	0·03
(R)-(−)-Cuparene (**1**)	2·31	2·18	0·13
Carvacryl acetate (**8**)	2·08	2·06	0·02
Thymyl acetate (**9**)	2·28	2·06	0·22
p-Cymene (**7**)	2·27	2·15	0·12

* $\Delta = CCl_4 - C_6D_6$.

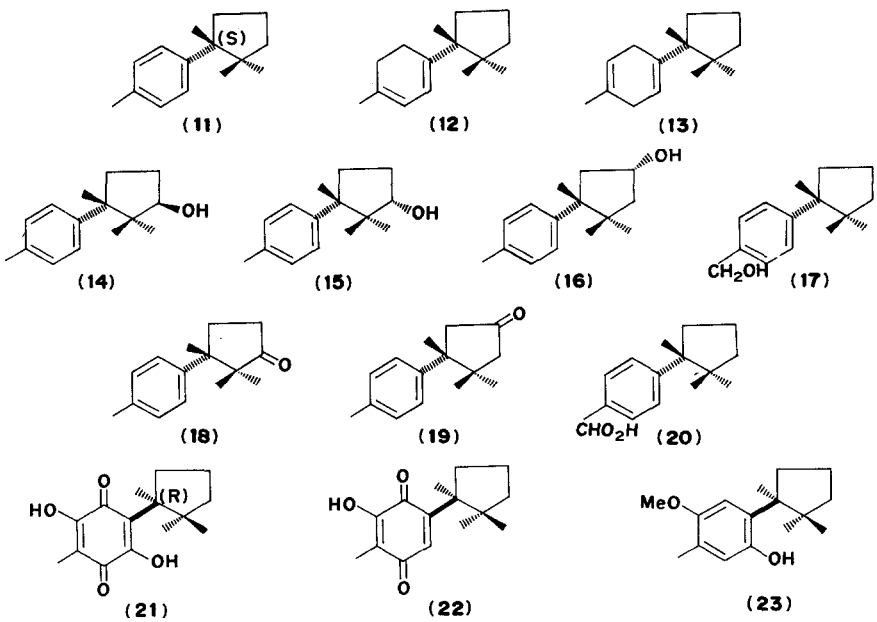
Synthesis of (*R*)-(−)-*δ-cuparenol* (**2**). Since (−)-*δ*-cuparenol (**2**) was isolated as a minor component from *B. pompeana*, the final proof of the structure and the elucidation of the absolute configuration was determined by synthesis from (R)-(−)-cuparene (**1**) isolated from the same liverwort. (R)-(−)-Cuparene (**1**) was submitted to Friedel–Craft acylation with MeCOCl and $AlCl_3$ in CS_2 to give 2-acetyl cuparene (**5**). In this case the acetyl group was introduced into the *ortho* position of the aromatic methyl group, because 2-acetyl *p*-cymene (**10**) would be obtained from the acetylation of *p*-cymene (**7**) [11]. The acetyl cuparene (**5**) was then rearranged, by Baeyer–Villiger reaction with CF_3CO_3H, into 2-acetoxy cuparene (**4**), whose hydrolysis with K_2CO_3 afforded (−)-2-hydroxy cuparene (**2**). 2-Hydroxy cuparene (**2**) and its acetate (**4**) thus synthesized were, respectively, identical with naturally occurring (−)-*δ*-cuparenol (**2**) and its acetate (**4**) by IR, PMR and MS comparison. The optical rotation ($[\alpha]_D$ −55·0°) of 2-hydroxy cuparene synthesized was the same ($[\alpha]_D$ −73·5°) as that of (−)-*δ*-cuparenol. Therefore, it was concluded that the stereostructure of (−)-*δ*-cuparenol isolated from the liverwort has the same chirality as the starting compound, (R)-(−)-cuparene (**1**).

At the present time many cuparene-type sesquiterpenoids have been isolated from the plant kingdom and their structures determined. Among them, the compounds, cuparene (**11**), α- cuprenene (**12**), *β*-cuprenene (**13**), α-cuparenol (**14**), α-iso-cuparenol (**15**), *β*-cuparenol (**16**), *γ*-cuparenol (**17**), α-cuparenone (**18**), *β*-cuparenone (**19**) and cuparenic acid (**20**) [7, 9, 12], show a positive optical rotation and have S-chirality. However, three compounds isolated from the fungus, *Helicobasidium mompa*, helicobasidin (**21**), deoxy-helicobasidin (**22**) and a phenol (**23**) [13–15], show a negative optical rotation and R-chirality. (−)-Cuparenc (**1**) and (−)-*δ*-cuparenol (**2**) isolated from a liverwort can now be added to the group of naturally occurring R-chirality cuparene-type sesquiterpenoids as new members.

EXPERIMENTAL

IR spectra were measured in CCl_4 or as a liquid film, and the PMR spectra in CCl_4 or C_6D_6 on a 60 MHz spectrometer using TMS. MS were determined on both single and double focusing instruments: 80 eV ionization chamber voltage, 80 μA total emmission, 1800 eV accelerating voltage and 200° ionization chamber temp. Optical rotations were determined with an automatic polarimeter in $CHCl_3$ and UV spectra in EtOH.

Isolation of (*R*)-(−)-*cuparene* (**1**). *B. pompeana* was collected in adjacent forests of Hiroshima City. The plant, after being air-dried was steam-distilled to give an oil (15 g, yield 1·2%; $[\alpha]_D^{25}$ +34·7°, n_D^{25} 1·5053, d_4^{25} 0·9397), which was fractionated into 15 fractions through a small-type spinning-band distillation apparatus. The 14th fraction, after being chromatographed on Si gel with hexane, was subjected to preparative GLC with a TC instrument (column 4 mm × 3 m, 10% PEG 20M on Chromosorb AW) to isolate (R)-(−)-cuparene (**1**) as



a colorless oily substance in *ca* 6% yield. $C_{15}H_{22}$(M^+ 202); $[\alpha]_D$ −27·6° (c 3·6); ν_{max}^{liq} 1515, 1385, 1375, 1365, 1220, 1195, 1070, 1020, 815, 760 cm^{-1}; λ 260, 265, 273 nm (ϵ, 250, 355, 340); MS *m/e* 41 (15%), 55 (7), 91 (23), 105 (25), 119 (33), 132 (100), 145 (40), 159 (15), 187 (5), 202 (M^+, 35).

Isolation of (R)-(−)-δ-cuparenol (**2**). The last fraction showing a positive phenol color reaction was repeatedly chromatographed over Si gel with hexane–EtOAc (4:1) to isolate (R)-(−)-δ-cuparenol (**2**) as a colorless oil in a yield of *ca* 0·5% for the total oil. $C_{15}H_{22}O$ (M^+ 218·1660); $[\alpha]_D$ −73·5° (c 0·6); 3,5-dinitrobenzoate, mp 171·5–172·5° (sealed tube); ν_{max} 3350, 1620, 1580, 1505, 1455, 1410, 1385, 1375, 1365, 1240, 1180, 1110, 880, 805 cm^{-1}; MS *m/e* 41 (25), 55 (17), 91 (23), 107 (23), 121 (25), 136 (100), 148 (83), 161 (27), 175 (5), 187 (5), 202 (5), 218 (M^+, 55).

Ozonolysis of (R)-(−)-cuparene (**1**). (R)-(−)-Cuparene (**1**) (200 mg) was ozonolyzed in MeOH (10 ml) for 30 hr at 20°. Solvent was evaporated *in vacuo* and the residue refluxed with an aq. soln of NaOH (5%, 2 ml) and H_2O_2 (30%, 0·3 ml) for 1 hr. The reaction mixture, after being extracted with Et_2O, was acidified with dil HCl and again extracted with Et_2O. The ether soln was dried and evaporated to give solid (R)-(−)-camphonanic acid (**3**) (30 mg), which was further purified by Si gel chromatography using hexane–EtOAc (1:1). $C_9H_{16}O_2$ (M^+ 156); m.p. 190°; $[\alpha]_D$ −13·2° (c 0·4); ν_{max} 3500–2500, 1700, 1410, 1390, 1375, 1370, 1300, 1230, 1100, 940 cm^{-1}; MS *m/e* 41 (85%), 55 (67), 70 (100), 87 (22), 95 (15), 111 (8), 138 (3), 156 (M^+, 4).

Acetylation of (R)-(−)-δ-cuparenol (**2**). To a soln of (R)-(−)-δ-cuparenol (**2**) (50 mg) in dry C_5H_5N (2 ml), Ac_2O (30 mg) was added and the mixture was allowed to stand at 20° for 18 hr. The reaction mixture, after being poured into ice H_2O, was extracted into Et_2O. The Et_2O soln was washed with dil HCl and then H_2O, and evaporation of the solvent gave δ-cuparenyl acetate (**4**) (30 mg) as a viscous oily substance. The product was further purified by Si gel chromatography using hexane–EtOAc (4:1). $C_{17}H_{24}O_2$ (M^+ 260); λ_{max} 263, 272 nm (ϵ, 1890, 950); ν_{max} 1770, 1510, 1215, 1015 cm^{-1}; δ 0·56 (3H, *s*), 1·02 (3H, *s*), 1·22 (3H, *s*), 1·50–1·80 (6H), 207 (3H, *s*), 2·19 (3H, *s*), 6·95 (2H, br *d*, *J* 9·5 Hz), 7·02 (1H, br *s*); MS *m/e* 44 (90%), 55 (37), 69 (23), 77 (34), 91 (46), 105 (37), 121 (37), 138 (82), 148 (100), 161 (42), 203 (15), 218 (48), 245 (5), 260 (M^+, 31).

Friedel–Craft acylation of (S)-(−)-cuparene (**1**). To a mixed soln of (S)-(−)-cuparene (**1**) (50 mg) and $AlCl_3$ (40 mg) in CS_2 (2 ml) in an ice bath, MeCOCl (30 mg) was added with continuous stirring and the reaction continued for 5 hr at 20°. The reaction mixture, after being poured into ice H_2O, was extracted with Et_2O. After removal of solvent 2-acetyl cuparene (**5**) (37 mg) was obtained as a light brown oily substance, which was then purified by Si gel chromatography using hexane–EtOAc (20:1). $C_{17}H_{24}O$ (M^+ 244); υ_{max} 1690, 1610, 1500, 1380, 1360, 1270, 1245, 955, 825 cm^{-1}; δ 0·57 (3H, *s*), 1·07 (3H, *s*), 1·18 (3H, *s*), 2·43 (3H, *s*), 2·47 (3H, *s*), 7·05 (1H, *d*, *J* 8 Hz), 7·28 (1H, *dd*, *J* 8, 2 Hz), 7·61 (1H, *d*, *J* 2 Hz); MS *m/e* 43 (100), 55 (36), 69 (14), 77 (13), 91 (23), 105 (14), 137 (21), 145 (27), 159 (47), 174 (41), 201 (9), 229 (31), 244 (M^+, 31).

Baeyer–Villiger rearrangement of 2-acetyl cuparene (**5**). To a soln of 2-acetyl cuparene (**5**) (35 mg) in CH_2Cl_2 (2 ml), finely ground $NaHPO_4$ (300 mg) was added. To this suspension a soln of CF_3CO_3H, prepared by adding a CH_2Cl_2 (2 ml) soln of $(CF_3CO)_2O$ (50 mg) to a mixture of 80% H_2O_2 (10 mg) and CH_2Cl_2 (1 ml), was added dropwise. The mixture, after being refluxed for 1 hr, was allowed to stand for 24 hr at 20°. The ppt. thus formed was filtered off and the filtrate washed with $NaHSO_3$ soln, H_2O, $KHCO_3$ soln and H_2O. The soln was dried and concentrated to give a viscous product, which was further purified by Si gel chromatography using hexane–EtOAc (20:1) to give a rearranged 2-acetoxy cuparene (**4**) (25 mg). The IR, PMR and MS were identical with those of δ-cuparenyl acetate (**4**) prepared from naturally occurring (R)-(−)-δ-cuparenol (**2**).

Hydrolysis of 2-acetoxy cuparene (**4**) *into (R)-(−)-2-hydroxy cuparene* (**2**). The rearranged ester (**4**) (25 mg) was added to a soln of K_2CO_3 (70 mg) in H_2O (0·4 ml) and MeOH (1 ml) and the mixture refluxed for 2 hr. The reaction mixture, after being concentrated *in vacuo*, was extracted with Et_2O. The Et_2O soln was washed with dil HCl and H_2O, dried and the solvent evaporated. The hydrolysis product thus obtained was then chromatographed on Si gel with hexane–EtOAc (1:1) to give (R)-(−)-2-hydroxy cuparene (**2**) (10 mg) as an oily substance. $C_{15}H_{22}O$ (M^+ 218); $[\alpha]_D$ −55·0° (c 0·2). The IR, PMR and MS spectra were superimposable with those of naturally occurring (R)-(−)-δ-cuparenol (**1**).

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