Data on Glu(OMe)[2]-litorin and intermediates obtained during the synthesis*

Number	Formula	Method[a]	Reaction solvent[b]	Crystallization solvent[c]	Melting point[d]	Optical rotation[e]	TLC[f] Rf_A	Rf_B	Rf_C	Rf_D
I	$C_{25}H_{36}N_6O_5S$	DCCI + HOTB	DMF	MeOH-Et_2O	163 °C	− 11.5°	–	0.06	0.59	0.94
II	$C_{20}H_{28}N_6O_3S \cdot HCl$	HCl	AcOH	MeOH-Et_2O	~ 170 °C	− 2.3°	–	–	0.23	0.70
III	$C_{23}H_{35}N_5O_7$	MA	THF	AcOEt-Et_2O	140–141 °C	− 4.7°	0.46	0.71	0.91	0.96
IV	$C_{15}H_{29}N_5O_5$	H_2	MeOH	AcOEt-Et_2O	155 °C	− 18.8°	–	0.02	0.52	0.88
V	$C_{34}H_{45}N_7O_8$	MA	THF	MeOH-Et_2O	195 °C	− 14.7°	0.49	0.67	0.91	1.00
VI	$C_{26}H_{39}N_7O_6$	H_2	MeOH + DMF	DMF-Et_2O	105 °C	− 18.5°	–	0.03	0.72	0.84
VII	$C_{40}H_{54}N_8O_{11}$	ONp	DMF	–	–	–	–	0.33	–	–
VIII	$C_{32}H_{48}N_8O_9$	H_2	DMF	–	–	–	–	0.02	0.72	0.82
IX	$C_{42}H_{61}N_9O_{13}$	ONp	DMF	DMF-H_2O	195 °C	− 26.7°	–	0.12	0.77	0.87
X	$C_{32}H_{44}N_9O_9$	HCOOH	–	–	–	–	–	–	0.41	0.84
XI	$C_{52}H_{68}N_{13}O_{12}S$	N_3	DMF	–	–	–	–	–	0.12	0.77

Amino acid composition of acid hydrolizate of compound XI[g]: $Glu_{2.09}$, $Gly_{1.00}$, $Ala_{1.00}$, $Val_{1.05}$, $Met_{1.03}$, $Phe_{0.97}$, $His_{0.93}$

* All the products were checked for purity in TLC. Intermediates VII, VIII and X were not obtained homogeneous.
[a] DCCI + HOBT, activated ester prepared in situ from N,N′-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole; HCl, dry HCl (~ 1.3 N) for 30 min at room temperature; MA, mixed anhydride with N-methylmorfoline and ethylchlorocarbonate (activation time: 2 min at −15 °C); H_2, hydrogenation in the presence of 10% palladium-charcoal; ONp, p-nitrophenyl ester; HCOOH, 99% formic acid for 3.5 h in the presence of 2-mercapto-ethanol; N_3, azide prepared with n-butyl nitrite and dry HCl in tetrahydrofuran at −25 °C for 10 min. [b] DMF: dimethylformamide; AcOH: glacial acetic acid; THF: tetrahydrofuran; MeOH: methanol. [c] Et_2O: diethylether; AcOEt: ethyl acetate. [d] Capillary tube, uncorrected. [e] Optical rotations were measured at 22°, C = 1. The solvent used were MeOH for compound IV, and DMF for the others. [f] TLC on pre-coated silica gel plates (E. Merck) in the following solvent systems: A, benzene/ethyl acetate/acetic acid/water (100:100:20:10) (upper phase); B, benzene/ethyl acetate/acetic acid/water (100:100:40:15) (upper phase); C, n-butanol/acetic acid/water (40:10:10); D, chloroform/methanol/32% NH_4OH (65:45:20). [g] Trp in decomposed during acid hydrolysis (100 °C for 18 h).

procedure in anhydrous conditions[6]. The yield was very poor. The pure compound could be obtained by preparative chromatography on pre-coated silica gel plates 60 F_{254} (E. Merck, Darmstadt), using a mixture of n-butanol-acetic acid-water (4:1:1) as solvent. The synthetic peptide showed the same electrophoretic and chromatographic mobilities, the same degradative pattern and the same biological properties[7] as natural Glu(OMe)[2]-litorin[8–12].

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(−)-Dihydromylione A, a novel tetracyclic sesquiterpene ketone containing two conjugated cyclopropane rings, from Mylia taylorii (liverwort)

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Summary. A novel tetracyclic sesquiterpene ketone named (−)-dihydromylione A (**III**) was isolated from the liverwort, and the structure was determined together with the absolute configuration to be ent-5,10-cyclo-aromadendr-3-one by connecting the compound with co-occurring (−)-myliol (**II**).

In our investigation on constituents of the liverworts (Hepaticae), several enantiomeric sesquiterpenoids, which are antipodes of those from the higher plants, such as (−)-longiborneol, (−)-longifolene, (+)-α-himachalene, (−)-α-longipinene[1], (−)-maalioxide, (+)-cyclocolorenone[2], (−)-cuparene[3] and (−)-bicyclogermacrene[4] have been isolated. Recently, we have isolated a novel ent-1,10-seco-aromadendrene ketone, (−)-taylorione(**I**), from a leafy liverwort, Mylia taylorii (Hook.) Gray[5], and revised the structure of (−)-myliol, which had been isolated from the same plant, as ent-5,10-cyclo-aromadendrene

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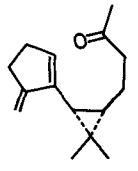
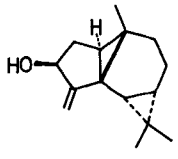
alcohol (**II**) based on the X-ray diffraction analysis[6]. Now, we wish to report the isolation and structural elucidation of a new additional sesquiterpene ketone of ent-5,10-cyclo-aromadendrane class, (−)-dihydromylione A (**III**), from the same liverwort.

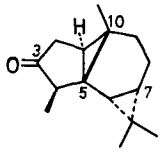
Material and methods. Mylia taylorii belonging to the Jungermanniaceae of liverwort contains 10–20 oil bodies in each cell of the gametophytes. The liverwort was collected at a forest in Kochi Prefecture, and the whole plant (1.1 kg) was digested with methanol after being dried in the shade for several days to obtain a brownish extract (23 g). A part (20 g) of the extract was first fractionated under a reduced pressure (2 mm Hg) to separate a sesquiterpenoid fraction (6 g) from the other portion. The elution chromatography of the distillate with silica gel and a mixed solvent of hexane and ethyl acetate (4:1) furnished a new ketone, (−)-dihydromylione A (50 mg), $C_{15}H_{22}O$ (M+ 218); $[\alpha]_D$ −34.1°;



(I)

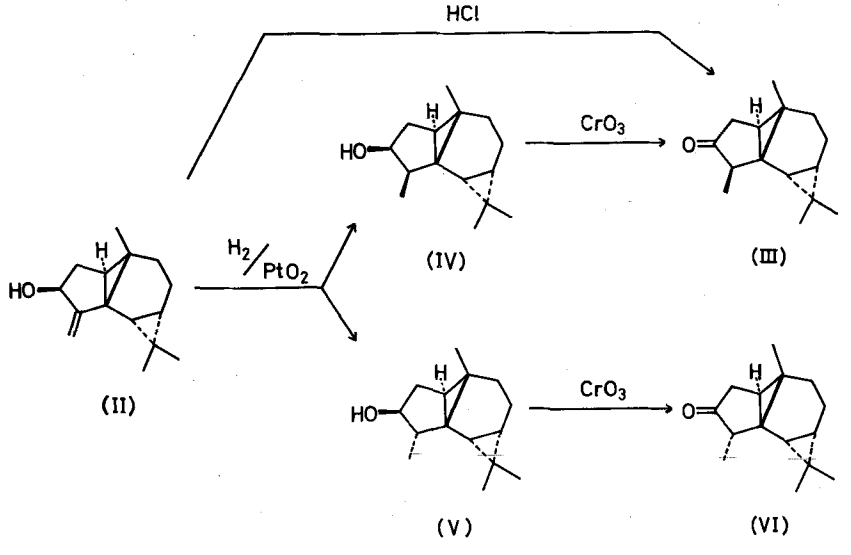


(II)



(III)

ν_{CCl_4} 3610, 3420, 1655, 898, 890 cm^{-1}; δ_{CCl_4} 0.92 (3H, s), 1.02 (6H, s), 4.63 (1H, br), 4.84, 5.08 (each 1H, d, J = 2.5), was hydrogenated with PtO_2 to give 2 dihydro-alcohols. These dihydro-alcohols were separated as less polar dihydromyliol A (**IV**), $C_{15}H_{24}O$ (M+ 220); m.p. 77–79°C; $[\alpha]_D$ −23.0°; ν_{KBr} 3440, 3040 cm^{-1}; δ_{CCl_4} 1.02, 1.03, 1.32 (each 3H, s), 1.07 (3H, d, J = 7), 4.51 (1H, sext, J = 9, 9, 2.5); $\lambda_{C_2H_5OH}$ 207 nm (ε 1010), 255 (200); R_f 0.22, and more polar dihydromyliol B (**V**), $C_{15}H_{24}O$ (M+ 220); m.p. 85–86°C; $[\alpha]_D$ −31.9°; ν_{KBr} 3210, 3055 cm^{-1}; δ_{CCl_4} 0.98 (6H, s), 1.07 (3H, s), 1.10 (3H, d, J = 7), 3.83 (1H, sext, J = 9, 9, 8.5); $\lambda_{C_2H_5OH}$ 207 nm (ε 1630); R_f 0.08, by preparative TLC in the proportion of 5/4, and they were characterized as the epimeric pair due to the newly formed secondary methyl, based on the fact that the secondary methyl of the less polar alcohol (53 Hz in 0.39 mM/M) exhibited larger down-field shift than that of the more polar alcohol (40 Hz in 0.42 mM/M) under admixing with Eu(fod)$_3$ shift reagent: the methyl of dihydromyliol A was in cis-configuration and that of dihydromyliol B in trans-configuration against the β-oriented secondary hydroxy group. The dihydroalcohols thus obtained were then oxidized with Sarett reagent to afford respectively dihydromylione A (**III**), $C_{15}H_{22}O$ (M+ 218); $[\alpha]_D$ −42.5°; ν_{CCl_4} 1740, 1413 cm^{-1}; δ_{CCl_4} 0.93, 1.08, 1.15 (each 3H, s), 1.16 (3H, d, J = 7); $\lambda_{C_2H_5OH}$ 202 nm (ε 2730), 262 (6640); $[\theta]_{320}$ + 80, and dihydromylione B (**VI**), $C_{15}H_{22}O$ (M+ 218); $[\alpha]_D$ −26.2°; ν_{CCl_4} 1740, 1413



(II) (IV) (III) (V) (VI)

$\lambda_{C_2H_5OH}$ 203 nm (ε 2700), 263 (6620), as a minor oily compound and 2 known compounds, (−)-taylorione (840 mg) and (−)-myliol (210 mg). The structural determination of the new sesquiterpene ketone was performed based on chemical and spectral data and further by connecting with (−)-myliol.

Results and discussion. The IR and PMR spectra exhibited the presence of three tertiary methyls (ν_{CCl_4} 1383, 1373 cm^{-1}; δ_{CCl_4} 0.92, 1.06, 1.12, each 3H, s), a secondary methyl (δ 1.13, 3H, d, J = 7) and a cyclic 5-membered ketone (ν 1740) containing an adjacent active methylene (ν 1412). The above results suggested that the carbon skeleton of this ketone may be the same tetracyclic one as that of (−)-myliol.

This structural deduction was confirmed by preparation of the ketone from the co-occurring compound, (−)-myliol. (−)-Myliol, $C_{15}H_{22}O$; m.p. 111–112°C; $[\alpha]_D$ −20.0°; $\lambda_{C_2H_5OH}$ 203 nm (ε 4300), 217 (4290), 263 (2750); ν_{CCl_4} 3610, 3420, 1655, 898, 890 cm^{-1}; δ_{CCl_4} 0.90, 1.03, 1.06 (each 3H, s), 1.14 (3H, d, J = 7); $\lambda_{C_2H_5OH}$ 210 nm (ε 1000), 260 (250); $[\theta]_{301}$ + 130. The spectra of the former coincided with those of the natural product.

(−)-Dihydromylione A was also obtained directly in treatment of (−)-myliol with methanolic HCl at room temperature for 6 h[7,8].

Thus, the structure and absolute configuration of (−)-dihydromylione A isolated from the liverwort should be represented by ent-5,10-cyclo-aromadendr-3-one (**III**).

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