Structures of Two New Halochamigrene Derivatives from the Red Alga *Laurencia nipponica* Yamada[1)]

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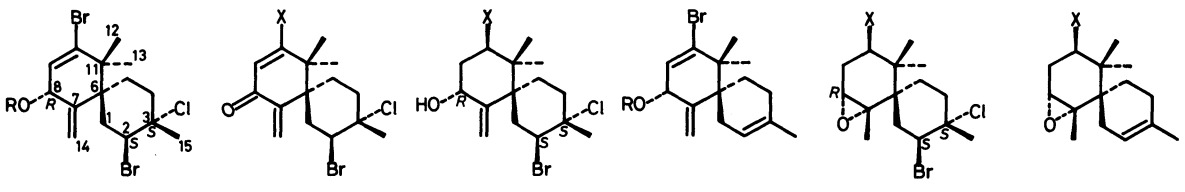
Synopsis. The structures of two new halochamigrene derivatives isolated from the title alga were determined by chemical and spectral methods.

We have previously reported the structures of the halogenated chamigrene derivatives which have been isolated from the red alga *Laurencia nipponica* Yamada, collected at Soya point, Hokkaido.[2)] Further investigation of this alga has yielded two new metabolites, a halogenated sesquiterpene alcohol **1** and a ketone **2**. We wish to describe herein the structures of these metabolites.

The sesquiterpene alcohol **1**, $C_{15}H_{21}OBr_2Cl$, oil, $[\alpha]_D^{20}$ −24.2° ($CHCl_3$), showed in its ^1H NMR spectrum broad signals at δ 0.99 (3H), 1.17 (3H), 4.27 (1H, m), 4.60 (1H, m), 5.06 (1H), 5.67 (1H), and 6.07 (1H), and a sharp singlet at δ 1.71 (3H). The ^{13}C NMR spectrum revealed no other double bonds, apart from those of an *exo*-methylene group at δ 144.4 (s) and 111.8 (t) and a trisubstituted double bond at 137.2 (s) and 130.9 (d), and hence **1** had to be a bicyclic alcohol. Acetylation of **1** with acetic anhydride and pyridine gave the corresponding acetate **3**, $C_{17}H_{23}O_2Br_2Cl$. Oxidation of **1** with pyridinium chlorochromate in CH_2Cl_2 afforded an α,β-unsaturated ketone which was identical with the natural ketone **2**, $C_{15}H_{19}OBr_2Cl$. The ^1H NMR spectrum of **2** exhibited pairs of signals very similar to those of the dienone **4**,[2)] derived from 2,10-dibromo-3-chlorochamigra-7(14)-en-8-ol (**5**). However, these pairs of signals, when the spectrum was measured at 100°C (in toluene-d_8), collapsed into singlets and the spectral change with temperature variation was reproducible. This fact suggests that the ketone **2** exists as two conformers equilibrated slowly at room temperature. Treatment of **1** with zinc and AcOH in MeOH yielded a monobromo alcohol **6**, $C_{15}H_{21}OBr$, which gave the acetate **7**, $C_{17}H_{23}O_2Br$. The ^1H NMR spectrum of **6** showed the presence of two quaternary methyl groups at δ 0.92 and 1.16 (each 3H, s), a vinyl methyl group at δ 1.60 (3H, br s), an *exo*-methylene group at δ 5.08 and 5.30 (each 1H, s), two olefinic protons at δ 5.38 (1H, m) and 6.17 (1H, d, J=4.5 Hz), and a proton α to hydroxyl group at δ 4.48 (1H, dd, J=4.5, 4.5 Hz), thus indicating that the vicinal bromine and chlorine atoms in **1** were eliminated to form an additional trisubstituted double bond bearing a methyl group. Spin decoupling experiments on the ^1H NMR spectrum of **6** showed the presence of $CH_2{=}\underset{|}{C}{-}CH(OH){-}CH{=}\underset{|}{C}-$ and $-CH_2{-}CH{=}C(CH_3)-$ moieties in the molecule. Comparison of the ^1H NMR spectra of **6** and **7** with those of previously described halochamigrene derivatives coupled with detailed analysis of the spectral data of **2** and **4** allowed us to propose formulae **1** and **2** for the sesquiterpene alcohol and the ketone, respectively. Confirmation of the structures **1** and **2** was obtained by the following chemical correlation with 2,10-dibromo-3-chloro-7,8-epoxychamigrane (**8**), the major metabolite of Atsuta's *L. nipponica*.[3)] Treatment of **8** with zinc and AcOH in MeOH gave three products, **9**, **10**, and **11**. The product **9**, $C_{15}H_{24}OBrCl$, revealed ^1H NMR spectrum very similar to that of **8** except for the chemical shifts of the *gem*-dimethyls and lack of the signal corresponding to the bromomethine proton at δ 4.10. The two signals due to the *gem*-dimethyl group (δ 0.84 and 0.88) in **9** were observed at higher magnetic field region than that (δ 0.96 and 1.10) in **8**, thus indicating that the bromine atom at C-10 of **8** was reduced in a way similar to the case of glanduliferol.[4)] The acid-catalyzed isomerization of **9** with *p*-toluenesulfonic acid in warm benzene gave an alcohol **12**, $C_{15}H_{24}OBrCl$; ν_{max} 3630, 1640, and 910 cm^{-1}. On the other hand, hydrogenation of **1** with PtO_2 in EtOAc gave the hydrogenated product, with evolution of hydrogen bromide, which was identical with **12** in all respects. Consequently, the structures of **1** and **2** were established as (2*S*,3*S*,8*R*)-2,10-dibromo-3-chlorochamigra-7(14),9-dien-8-ol and (2*S*,3*S*)-2,10-dibromo-3-chlorochamigra-7(14),9-dien-8-one, respectively. Conformational analyses of **1** and **2** are in progress.

Experimental

The melting points were uncorrected. The IR spectra were measured on a JASCO A-102 spectrometer and the UV spectra on a Shimadzu UV-240 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-FX 100 spectrometer. TMS was used as an internal reference in $CDCl_3$. The low and



high resolution mass spectra were obtained at 70 eV with a JEOL JMS-D300 spectrometer. The optical rotations were measured on a JASCO DIP-140 polarimeter in $CHCl_3$.

Isolation. The detail of the separation of the extracts has been described in the previous paper.[2] The ethyl acetate fraction obtained by alumina column chromatography of the extracts was repeatedly chromatographed on silica-gel column to yield **1** (4% of the extracts) along with two halochamigrene derivatives[2] and *trans*-deacetylkumausyne.[5] From the benzene fraction **2** was isolated in 1.5% yield by repeated silica-gel column chromatography together with kumausallene[6] and *trans*-kumausyne.[5]

1: Colorless oil; $[\alpha]_D^{20}$ −24.2° (*c* 1.88); UV (EtOH), λ_{max} 203 nm (ε 8500); IR (film), ν_{max} 3350, 1640, 1390, 1380, 1367, 1300, 1100, 1045, 990, 910, 860, 810, and 750 cm^{-1}; ^1H NMR, in the text; ^{13}C NMR (25.0 MHz), δ=23.0 (q), 23.5 (q), 24.0 (q), 25.9 (t), 38.6 (t×2), 47.0 (s), 50.1 (s), 60.6 (d), 69.0 (d), 71.7 (s), 111.8 (t), 130.9 (d), 137.2 (s), and 144.4 (s); MS, *m/z* (rel. intensity) 416, 414, 412, 410 (0.2:1:1.5:0.5; M^+), 335, 333, 331 (13:48:37; M^+−Br), 297, 295 (16:17; M^+−Br-HCl), 215 (40; M^+−Br-HCl-HBr), 147 (32), 119 (50), 97 (51), 91 (48), 81 (48), 69 (69), 57 (77), 55 (79), 43 (78), and 41 (100). Found: *m/z* 333.0445. Calcd for $C_{15}H_{21}O^{81}Br^{35}Cl$: M−Br, 333.0445.

2; Pale yellow oil; $[\alpha]_D^{22}$ +1.95° (*c* 1.59); UV (EtOH), λ_{max} 262 (ε 9700) and 202 (6200) nm; IR (film), ν_{max} 1670, 1620, 1595, 1390, 1380, 1370, 1320, 1290, 1260, 1220, 1180, 1150, 1100, 1065, 950, 890, 870, and 760 cm^{-1}; ^1H NMR, δ=1.11, 1.14 (total 3H, s), 1.37 (3H, s), 1.69 (3H, s), 4.21 (0.4H, dd, *J*=12, 5 Hz), 4.64 (0.6H, dd, *J*=13, 5 Hz), 5.45 (1H, s), 6.21 (1H, s), 6.52 (0.6H, s), and 6.54 (0.4 H, s); MS, *m/z* 414, 412, 410, 408 (3:16:22:10; M^+), 377, 375, 373 (0.9:2:1; M^+−Cl), 333, 331, 329 (26:100:78; M^+−Br), 296, 294 (9:11; M^+−Br-Cl), 295, 293 (52:53; M^+−Br-HCl), 252, 250 (10:30; M^+−Br-Br), 251, 249 (12:20; M^+−Br-HBr), 215 (41; M^+−Br-Br-Cl), 214 (63; M^+−Br-Br-HCl), 213 (71; M^+−Br-HBr-HCl), 149 (61), 95 (66), 67 (68), and 41 (78). Found: *m/z* 409.9470. Calcd for $C_{15}H_{19}O^{79}Br^{81}Br^{35}Cl$: M, 409.9472.

Acetylation of 1. Acetylation of **1** (19 mg) was carried out with acetic anhydride (0.3 ml) and pyridine (0.3 ml) in the usual manner. The acetylated product was purified by a silica-gel plate to give **3** (17 mg); oil; $[\alpha]_D^{20}$ −71.7° (*c* 0.53); IR (film), ν_{max} 1740, 1640, 1230, 1100, 1040, 1010, 990, 930, 920, and 900 cm^{-1}; ^1H NMR, broad and complex signals; MS, *m/z* 458, 456, 454, 452 (0.3:1.1:1.3:0.6; M^+) and 416, 414, 412, 410 (5:25:35:16; M^+−CH_2CO). Saponification of **3** with K_2CO_3 in MeOH gave the original alcohol **1** in quantitative yield.

PCC Oxidation of 1. To a suspended solution of pyridinium chlorochromate (10 mg) in CH_2Cl_2 (0.5 ml) was added a solution of **1** (12 mg) in CH_2Cl_2 (0.5 ml). The mixture was stirred for 40 min at room temperature and then worked up in the usual manner. The resulting oil was chromatographed on a silica-gel plate to afford **2** (10 mg); pale yellow oil; $[\alpha]_D^{23}$ +1.68° (*c* 1.28); whose spectral data were consistent with those of the natural ketone **2**.

Treatment of 1 with Zn-dust-AcOH. To a solution of **1** (10 mg) in MeOH (0.4 ml) was added activated Zn-dust (50 mg) and AcOH (0.04 ml). The mixture was stirred for 70 h at room temperature and then filtered to remove the Zn-dust. The filtrate was extracted with ether. The ethereal solution was successively washed with water, 5% aqueous $NaHCO_3$, and water, and dried over Na_2SO_4. The subsequent removal of the solvent gave a residual oil, which was chromatographed on a silica-gel plate to give **6** (4 mg); crystals; mp 58—59°C; $[\alpha]_D^{20}$ −95.8° (*c* 0.45); IR ($CHCl_3$), ν_{max} 3600, 3400, 1640, 1010, 990, 915, and 895 cm^{-1}; ^1H NMR, in the text; MS, *m/z* 298, 296 (3:3; M^+) and 280, 278 (56:58; M^+−H_2O).

Acetylation of 6. Acetylation of **6** (3 mg) was carried out with acetic anhydride (0.15 ml) and pyridine (0.15 ml) at room temperature by the usual method to give **7** (3 mg); oil; $[\alpha]_D^{25}$ −103° (*c* 0.25); IR ($CHCl_3$), ν_{max} 1730, 1640, 1230, 1015, 973, and 915 cm^{-1}; ^1H NMR, δ=0.92 (3H, s), 1.18 (3H, s), 1.59 (3H, br s), 2.04 (3H, s), 5.14 (1H, s), 5.30 (1H, m), 5.49 (1H, s), 5.61 (1H, d, *J*=5 Hz), and 6.12 (1H, d, *J*=5 Hz); MS, *m/z* 340, 338 (0.3:0.3; M^+) and 280, 278 (41:42; M^+−CH_3COOH).

Treatment of 8 with Zn-dust-AcOH. To a solution of **8** (46 mg) in MeOH (1.5 ml) was added activated Zn-dust (200 mg) and AcOH (0.15 ml). The mixture was stirred for 6 h at room temperature and then worked up in a manner similar to the case of **1**. The resulting oil was chromatographed on a silica-gel column to give **9** (6 mg); crystals; mp 114—115°C; $[\alpha]_D^{21}$ +16.8° (*c* 0.46); IR ($CHCl_3$), ν_{max} 1150, 1105, 1090, and 1055 cm^{-1}; ^1H NMR, δ=0.84 (3H, s), 0.88 (3H, s), 1.54 (3H, s), 1.71 (3H, s), 2.97 (1H, dd, *J*=2, 2 Hz), and 4.90 (1H, dd, *J*=12, 6 Hz); MS, *m/z* 338, 336, 334 (0.2:1:0.9; M^+) and 257, 255 (3:13; M^+−Br); **10** (9 mg); oil; $[\alpha]_D^{18}$ −81.1° (*c* 0.76); ^1H NMR, δ=0.93 (3H, s), 0.99 (3H, s), 1.31 (3H, s), 1.67 (3H, br s), 2.88 (1H, dd, *J*=2, 2 Hz), 4.38 (1H, dd, *J*=12, 6 Hz), and 5.42 (1H, m); MS, *m/z* 300, 298 (0.7: 0.8; M^+) and 219 (28; M^+−Br); **11** (6 mg); oil; $[\alpha]_D^{21}$ −77.5° (*c* 0.46); ^1H NMR, δ=0.76 (3H, s), 0.81 (3H, s), 1.29 (3H, s), 1.67 (3H, br s), 2.89 (1H, dd, *J*=2, 2 Hz), and 5.43 (1H, m); MS, *m/z* 220 (4; M^+).

Isomerization of 9. To a solution of **9** (4 mg) in benzene (0.5 ml) was added a piece of TsOH, and the mixture was stirred for 35 min at 60°C, cooled, and extracted with ether. The ethereal solution was washed with 5% aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and then evaporated to leave a residual oil, which was chromatographed on a silica-gel plate to give **12** (2 mg); oil; $[\alpha]_D^{18}$ −29.4° (*c* 0.19); IR ($CHCl_3$), ν_{max} 3630, 1640, 1300, 1100, and 910 cm^{-1}; ^1H NMR, δ=0.82, 0.94, 1.70 (each 3H, s), 4.32 (1H, m), 4.37 (1H, dd, *J*=13, 4 Hz), 4.93 (1H, s), and 5.59 (1H, s); MS, *m/z* 338, 336, 334 (0.2:0.8:1; M^+) and 320, 318, 316 (0.8:1.3:1; M^+−H_2O).

Hydrogenation of 1. Hyrogenation of **1** (8 mg) was performed in EtOAc over PtO_2-catalyst. After removal of the catalyst and the solvent, the residual oil was chromatographed on a silica-gel plate to give **12** (3 mg); oil; $[\alpha]_D^{23}$ −31.9° (*c* 0.31); the spectral data were identical with those of **12** derived from **9**.

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