Structures of Halogenated Chamigrene Derivatives, Minor Constituents from the Red Alga *Laurencia nipponica* Yamada[1]

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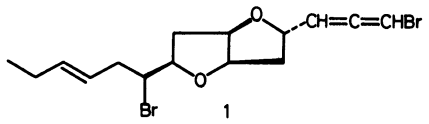
Three halogenated chamigrane-type sesquiterpenes have been isolated as the minor metabolites from the red alga *Laurencia nipponica*, collected at Sannai, near Wakkanai. The absolute structures of these compounds were confirmed by spectral and chemical methods.

In the course of our continuing studies on the constituents of the red alga *Laurencia nipponica* Yamada ("Ura-sozo") collected at various locations in warm and cold current regions in Hokkaido, the diversity of the secondary metabolites of this species has been found to be dependent upon growth localities.[2] As part of further investigations of this alga, we turned our attention to the specimens in Northern Hokkaido (Dohoku) and collected at Sannai, Soya point, near Wakkanai, Hokkaido. This specimen displayed the presence of kumausallene (**1**) and *trans*-kumausyne (**2**) as the principal metabolites, which have recently been isolated from *L. nipponica* collected at Kumausu, near Otaru, Hokkaido.[3] Furthermore, several known and unknown sesquiterpenes have also been isolated as the minor metabolites. In this paper we report the structures of three halogenated chamigrane-type sesquiterpenes.



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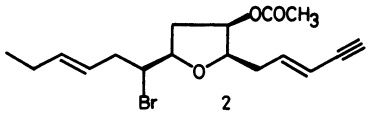

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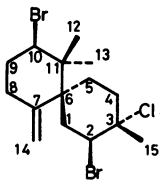
Repeated column chromatography of the neutral methanol extracts yielded a halogenated sesquiterpene hydrocarbon **3** (1.6% of the extracts)and halogenated sesquiterpene alcohols **4** (2.0%) and **5** (1.7%) along with kumausallene (**1**) (12%) and *trans*-kumausyne (**2**) (16%).

The halogenated sesquiterpene hydrocarbon, **3**, $C_{15}H_{23}Br_2Cl$ (*m/z* 402, 400, 398, and 396; M^+), mp 76—77 °C, $[\alpha]_D^{15}$ +30.6°, showed in its IR and ^1H NMR spectra the presence of a *gem*-dimethyl group [ν_{max} 1390 and 1380 cm^{-1}; δ 0.96 and 1.15 (each 3H, s)], a tertiary methyl group [δ 1.70 (3H, s)], two halomethine groups [δ 4.45 (1H, dd, J=12, 5 Hz) and 4.72 (1H, dd, J=12, 5 Hz)], and an exomethylene group [ν_{max} 1640 and 908 cm^{-1}; δ 4.87 and 5.26 (each 1H, s)]. Comparison of the ^1H and ^{13}C NMR spectra of **3** with those[4,5] of 2,10-dibromo-3-cholro-α-chamigrene (**6**) previously isolated from *L.* species,[4] seemed to indicate **3** to be 2,10-dibromo-3-chloro-β-chamigrene. Confirmation of the structure of **3** was obtained by the following chemical correlation. Hydrogenation of **3** over PtO_2 in ethanol gave the dihydro derivative which was identical with the hydrogenation product (**7**)[4b] of **6** in all respects, thus indicating that this compound is (2*S*)(3*S*)(10*R*)-2,10-dibromo-3-chloro-β-chamigrene (**3**). The IR, ^1H NMR, and mass spectral properties of **3** are almost identical with those of nidificene previously isolated from *L. nidifica*,[6] showing that these compounds appear to be the same material.[7]

One of the sesquiterpene alcohols, **4**, $C_{15}H_{23}OBr_2Cl$ (*m/z* 418, 416, 414, and 412; M^+), oil, $[\alpha]_D^{17}$ +3.33°, showed in its ^1H NMR spectrum the presence of three tertiary methyl groups, including *gem*-dimethyl group, at δ 0.91, 1.17, and 1.71 (each 3H, s), an α-proton to hydroxyl group at δ 4.43 (1H, dd, J=3, 3 Hz), two halomethine protons at 4.73 (1H, dd, J=13, 4 Hz) and 4.74 (1H, dd, J=11, 5.5 Hz), and exomethylene protons at 5.06 and 5.46 (each 1H, sharp s). Acetylation of **4** with acetic anhydride in pyridine afforded the corresponding acetate **8**, $C_{17}H_{25}O_2Br_2Cl$, ν_{max} 1740 and 1238



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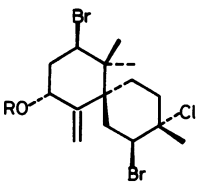
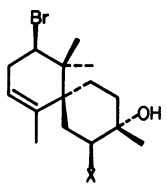
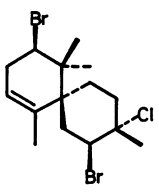


4: R=H
8: R=Ac



5: X=Br
11: X=Cl



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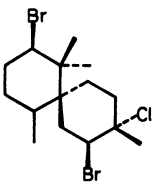

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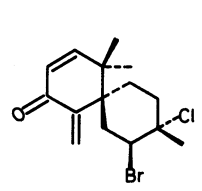

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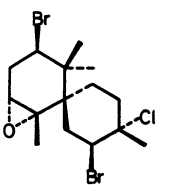

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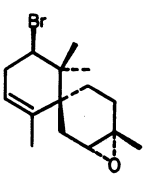

12

cm^{-1}; δ 5.41 (dd, J=4, 3 Hz), which regenerated the parent alcohol on mild saponification with K_2CO_3 in methanol. Furthermore, **4** was subjected to Jones or pyridinium chlorochromate oxidation to yield, with concomitant dehydrobromination, dienone **9**, $C_{15}H_{20}OBrCl$, ν_{max} 1672 cm^{-1}; λ_{max} 233 nm (ε 6300); δ 1.02, 1.05 (total 3H), 1.20 (3H, s), 1.69 (3H, s), 4.26 (0.4H, dd, J=12, 4 Hz), 4.69 (0.6H, dd, J=13, 5 Hz), 5.38 (1H, s), 5.95 (0.6H, d, J=10 Hz), 5.98 (0.4H, d, J=10 Hz), 6.16 (1H, s), and 6.51 (1H, d, J=10 Hz). The ^1H NMR spectrum of **9** suggests that this dienone exists at room temperature as an equilibrium mixture of two conformational isomers, which is supported by the observation of distinct temperature dependence in the ^1H NMR spectra (toluene-d_8) at various temperature.[8] In view of the above-mentioned data coupled with comparison of spectral properties of **3** and **4**, formula **4** could readily be proposed for this alcohol. The equatorial nature of the proton at C-8 was suggested by its J-values in the ^1H NMR spectra of **4** and **8**. The structure of **4**, including the absolute configuration, was established by derivation from 2,10-dibromo-3-chloro-7,8-epoxychamigrane (**10**) which was the major metabolite of Atsuta's *L. nipponica*.[4c,d] Treatment of **10** with *p*-toluenesulfonic acid in warm benzene gave **4** in 53% yield. Therefore, the structure of this alcohol is represented by formula **4**, which is the first example of halochamigrane derivatives from the genus *Laurencia* with a hydroxyl group at C-8.

Another sesquiterpene alcohol, **5**, $C_{15}H_{24}OBr_2$ (*m/z* 382, 380, and 378; M^+), oil, $[\alpha]_D^{18}$ −27.0°, revealed very similar IR, ^1H and ^{13}C NMR spectra to those of glanduliferol (**11**),[4b] indicating that **5** must be bromohydrin at C-2 and C-3 instead of chlorohydrin at C-2 and C-3 in glanduliferol (**11**). This was confirmed by the following reaction. Treatment of **5** with 5% methanolic KOH at room temperature gave 10-bromo-2,3-epoxy-α-chamigrene (**12**) as same as in the case of **11**.[4b] Recently Fukuzawa *et al.* reported that 2,10-dibromo-3-hydroxy-α-chamigrene has been isolated as a crystalline state (mp 58—59 °C, $[\alpha]_D^{20}$ −34.2°) from *L. nipponica* collected at the inside of Kabutoiwa, Oshoro Bay.[9] Unambiguously our alcohol was found to be identical with Fukuzawa's sample by comparison of the spectral data.

Previously we have isolated glanduliferol (**11**) from the specimen of *L. nipponica* (*L. glandulifera*)[10] collected at the outside of Kabutoiwa, Oshoro Bay, in August 1963 and 1964. The finding of 2,10-dibromo-3-hydroxy-α-chamigrene (**5**) from Oshoro's *L. nipponica* prompted us to reinvestigate the specimen collected at the outside of Kabutoiwa. Interestingly the specimens collected in 1978 (August)[11] and 1983 (June) revealed the presence of **5** instead of glanduliferol (**11**).

Experimental

The melting point was uncorrected. The IR spectra were measured on a JASCO A-102 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-FX100 spectrometer, TMS being used as an internal reference in $CDCl_3$. The UV spectra was obtained with a Shimadzu UV-240 spectrophotometer. The low and high resolution mass spectra were recorded on a JEOL JMS-D300 spectrometer. The optical rotations were measured on a JASCO DIP-140 polarimeter in $CHCl_3$. Aluminium oxide (Merck, activity II-III) and silica gel (Merck, Kieselgel 60, 70—230 mesh) were used for column chromatography. Silica gel 60 F_{254} (Merck) was used for thin-layer chromatography. All known compounds were identified by comparison of the spectral data with those of the authentic specimens.

Isolation. *Laurencia nipponica* Yamada was collected early in July, 1981, at Sannai, Soya point, near Wakkanai, Hokkaido. The neutral methanol extracts (2.0 g) (*ca.* 1% of the half-dried alga) obtained by the conventional methods were fractionated by column chromatography over alumina. The fraction eluted with hexane was rechromatographed on silica-gel column to yield isodihydrolaurene (7 mg),[4c] laurene (10 mg),[12] and α-bromocuparene (5 mg).[13] The fraction eluted with hexane–benzene (1 : 1) was further chromatographed on silica-gel column to yield 2,10-dibromo-3-chloro-β-chamigrene (**3**) (32 mg), selin-4(14)-en-5α-ol (30 mg),[14] and kumausallene (**1**) (100 mg).[3] The fraction eluted with benzene was further subjected to silica-gel column chromatography to give kumausallene (**1**) (140 mg) and *trans*-kumausyne (**2**) (320 mg).[3] The fraction eluted with ethyl acetate was repeatedly chromatographed on silica-gel column to give laurenisol (6 mg),[11] an unidentified alcohol (80 mg), 2,10-dibromo-3-chloro-8-hydroxy-β-chamigrene (**4**) (40 mg), 2,10-dibromo-3-hydroxy-α-chamigrene (**5**) (34 mg), and deacetylkumausyne (55 mg).[3]

2,10-Dibromo-3-chloro-β-chamigrene (3): Mp 76—77 °C (from hexane); $[\alpha]_D^{15}$ +30.6° (*c* 1.40); IR (CCl_4), ν_{max} 3080, 1640, 1390, 1380, 1306, 1295, 1200, 1158, 1093, 1060, 992, 970, 908, and 863 cm^{-1}; ^1H NMR, δ 0.96 (3H, s), 1.15 (3H, s), 1.70 (3H, s), 1.8—2.6 (10H, m), 4.45 (1H, dd, J=12 and 5 Hz), 4.72 (1H, dd, J=12 and 5 Hz), 4.87 (1H, s), and 5.26 (1H, s); ^{13}C NMR, δ 16.4 (q), 22.5 (q), 23.1 (q), 24.4 (t), 32.4 (t), 34.8 (t), 37.6 (t)×2, 42.7 (s), 50.0 (s), 60.3 (d), 62.5 (d), 70.7 (s), 113.6 (t), and 144.5 (s); MS (70 eV), *m/z* (rel intensity) 402, 400, 398, 396 (2 : 9 : 13 : 6; M^+), 387, 385, 383, 381 (1 : 4 : 6 : 3; M^+-CH_3), 321, 319, 317 (5 : 19 : 15; M^+-Br), 283, 281 (29 : 27; $M^+-Br-HCl$), 201 (47; $M^+-Br-HBr-HCl$), 109 (100), 95 (73), 69 (99), and 41 (99). Found: *m/z* 399.9855. Calcd for $C_{15}H_{23}{}^{79}Br^{81}Br^{37}Cl$: M, 399.9808.

2,10-Dibromo-3-chloro-8-hydroxy-β-chamigrene (4): Colorless oil; $[\alpha]_D^{17}$ +3.33° (*c* 1.20); IR (film), ν_{max} 3400, 3097, 1630, 1394, 1376, 1348, 1300, 1165, 1150, 1132, 1098, 1040, 1010, 975, 925, 895, 812, and 712 cm^{-1}; ^1H NMR, δ 0.91 (3H, s), 1.17 (3H, s), 1.71 (3H, s), 2.0—2.5 (9H, m), 4.43 (1H, dd, J=3 and 3 Hz), 4.73 (1H, dd, J=13 and 4 Hz), 4.74 (1H, dd, J=11 and 5.5 Hz), 5.06 (1H, s), and 5.46 (1H, s); ^{13}C NMR, δ 17.4 (q), 23.9 (q), 24.3 (q), 26.7 (t), 39.6 (t)×2, 42.4 (t), 43.8 (s), 50.8 (s), 60.1 (d), 61.6 (d), 71.9 (s), 76.0 (d), 118.1 (t), and 146.5 (s); MS, *m/z* 418, 416, 414, 412 (0.2 : 1 : 1.4 : 0.7; M^+), 400, 398, 396, 394 (0.5 : 2.3 : 3.3 : 1.4; M^+-H_2O), 380, 378, 376 (0.5 : 0.9 : 0.5; M^+-HCl), 347, 345, 343 (3 : 4.5 : 2; $M^+-H_2O-HCl-CH_3$), 337, 335, 333 (5 : 19 : 16; M^+-Br), 319, 317, 315 (11 : 46 : 35; M^+-H_2O-Br), 299, 297 (27 : 28; $M^+-Br-HCl$), 217 (17; $M^+-HBr-HCl-Br$), 199 (34; $M^+-Br-HBr-HCl-H_2O$), 157 (29), 147 (28), 119 (40), 107 (38), 105 (45), 93 (100), 91 (43), 69 (69), and 41 (89). Found: *m/z* 395.9686. Calcd for $C_{15}H_{21}{}^{79}Br^{81}Br^{35}Cl$: $M-H_2O$, 395.9681.

2,10-Dibromo-3-hydroxy-α-chamigrene (5): Colorless oil; $[\alpha]_D^{18}$ −27.0° (*c* 2.13); IR ($CHCl_3$), ν_{max} 3570, 1397, 1385, 1342, 1130, 1108, 1095, 1070, 1045, 1015, 990, 980, 928, and 837 cm^{-1}; ^1H NMR, δ 0.95 (3H, s), 1.23 (3H, s), 1.35 (3H, s), 1.98 (3H, finely splitted m), 1.5—2.3 (7H, m), 2.4—2.7 (2H, m), 4.56 (1H, dd, J=10 and 7.5 Hz), 4.77 (1H, dd, J=10 and 8.5 Hz),

and 5.21 (1H, m); ^{13}C NMR, δ 17.3 (q), 22.2 (q), 24.7 (q), 25.9 (q), 31.6 (t), 35.9 (t), 36.3 (t), 39.1 (t), 42.7 (s), 48.2 (s), 61.3 (d), 66.3 (d), 72.0 (s), 122.3 (d), and 140.1 (s); MS, *m/z* 382, 380, 378 (0.2 : 0.4 : 0.2 : M^+), 301, 299 (17 : 17; M^+-Br), 283, 281 (25 : 25; M^+-Br-H_2O), 201 (71; $M^+-Br-HBr-H_2O$), 159 (59), 149 (58), 147 (74), 145 (98), 133 (49), 119 (55), 109 (61), 105 (70), 93 (54), 91 (76), 69 (53), 55 (68), 43 (100), and 41 (97); Found: *m/z* 301.1007. Calcd for $C_{15}H_{24}O^{81}Br$: M−Br, 301.0992.

Hydrogenation of ***3***. The hydrogenation of **3** (12.6 mg) was performed in ethanol (2.0 ml) over PtO_2-catalyst. After removal of the catalyst and the solvent, the residual oil was chromatographed on a silica-gel plate to give **7** (7.0 mg); $[\alpha]_D^{21}$ +47.5° (*c* 0.65); The IR, ^{1}H NMR, and mass spectra were identical with those of authentic 2,10-dibromo-3-chlorochamigrane.[4b]

Acetylation of ***4***. Acetylation of **4** (12 mg) was carried out with acetic anhydride in pyridine in the usual manner. The acetylated product was purified by column chromatography on silica-gel to give **8** (11 mg); colorless oil; $[\alpha]_D^{17}$ −15.4° (*c* 0.34); IR (film), ν_{max} 3110, 1740, 1635, 1392, 1370, 1348, 1238, 1190, 1167, 1148, 1130, 1093, 1023, 930, 908, 877, 808, 730, and 715 cm^{-1}; ^{1}H NMR, δ 0.92 (3H, s), 1.19 (3H, s), 1.71 (3H, s), 2.02 (3H, s), 2.1—2.5 (8H, m), 4.61 (1H, dd, *J*= 12 and 6.5 Hz), 4.67 (1H, dd, *J*=13 and 5 Hz), 5.20 (1H, s), 5.41 (1H, dd, *J*=4 and 3 Hz), and 5.64 (1H, s); MS, *m/z* 458, 456, 454 (0.2 : 0.2 : 0.1; M^+), 418, 416, 414, 412 (0.1 : 0.4 : 0.6 : 0.3; $M^+-C_2H_2O$), 400, 398, 396, 394 (0.4 : 1.5 : 2 : 1; M^+-CH_3COOH), 379, 377, 375 (0.2 : 0.4 : 0.3; M^+-Br), 337, 335, 333 (0.2 : 0.5 : 0.5; $M^+-C_2H_2O-Br$), 319, 317, 315 (7 : 87 : 56; $M^+-Br-CH_3COOH$), 199 (27), 157 (13), 119 (19), 107 (22), 105 (25), 93 (15), 91 (20), 69 (27), 43 (100), and 41 (36).

Saponification of ***8***. A soln of **8** (2.7 mg) and potassium carbonate (9.6 mg) in methanol (0.3 ml) was allowed to stand at room temp for 20 min and then worked up in the usual way to give **4** (2.3 mg); The IR and ^{1}H NMR spectra were identical with those of natural alcohol (**4**).

PCC Oxidation of ***4***. To a suspended soln of pyridinium chlorochromate (10 mg) in CH_2Cl_2 (0.1 ml) was added a soln of **4** (16 mg) in CH_2Cl_2 (0.1 ml). The reaction mixture was allowed to stand at room temp for 2 h. After addition of ether, filtration, and washing with ether, the combined organic soln was passed through a short pad of Frorisil, and then the solvent was removed to leave a residual oil, which was chromatographed on a silica-gel plate to give **9** (4.1 mg) as a pale yellow oil; $[\alpha]_D^{20}$ −10.7° (*c* 0.38); UV (EtOH), λ_{max} 233 (ε 6300), and 200 nm (ε 5300); IR (film), ν_{max} 1672, 1620, 1397, 1385, 1352, 1315, 1253, 1220, 1162, 1095, 1065, 945, 845, 820, and 752 cm^{-1}; ^{1}H NMR, δ 1.02, 1.05 (each s, total 3H), 1.20 (3H, s), 1.69 (3H, s), 4.26 (0.4H, dd, *J*=12 and 4 Hz), 4.69 (0.6H, dd, *J*=13 and 5 Hz), 5.38 (1H, s), 5.95 (0.6H, d, *J*=10 Hz), 5.98 (0.4H, d, *J*=10 Hz), 6.16 (1H, s), and 6.51 (1H, d, *J*=10 Hz); MS, *m/z* 334, 332, 330 (5 : 18 : 16; M^+), 319, 317, 315 (1 : 5 : 4; M^+-CH_3), 297, 295 (3 : 3; M^+-Cl), 253, 251 (13 : 37; M^+-Br), 215 (79), 199 (62), and 96 (100).

Jones Oxidation of ***4***. To a soln of **4** (10.3 mg) in acetone (4.0 ml) was added two drops of Jones reagent. After the usual work-up, the residual oil was chromatographed on a silica-gel plate to give **9** (7.0 mg).

Conversion of ***10*** *into* ***4***. To a soln of **10** (32.4 mg) in benzene (0.5 ml) was added a piece of TsOH, and the mixture was stirred for 20 min at 60 °C (bath temp). The reaction mixture was worked up as usual to leave an oily residue, which was chromatographed on silica-gel column to give **4** (17.1 mg); $[\alpha]_D^{17}$ +3.94° (*c* 0.86); The IR, ^{1}H NMR, and mass spectra were identical with those of natural **4**.

Conversion of ***5*** *into* ***12***. A soln of **5** (4.9 mg) in 5% methanolic KOH (0.3 ml) was allowed to stand at room temp for 30 min. After being treated by the usual method, the resulting oil was purified by chromatography on a silica-gel plate to afford **12** (3.8 mg); $[\alpha]_D^{20}$ −75.6° (*c* 0.21); The IR and ^{1}H NMR spectra were identical with those of authentic 10-bromo-2,3-epoxy-α-chamigrene.[4b]

We are grateful to Prof. K. L. Erickson, Clark University, for the spectral data of nidificene, and also to Dr. Akio Fukuzawa, Hokkaido University, for the spectral data of 2,10-dibromo-3-hydroxy-α-chamigrene and valuable suggestions.

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