September, 1988] © *1988 The Chemical Society of Japan* NOTES *Bull. Chem. Soc. Jpn., 61, 3371—3373 (1988)*

The Structure and Absolute Stereochemistry of a Halogenated Chamigrene Derivative from the Red Alga *Laurencia* Species[1)]

Minoru Suzuki,* Etsuro Kurosawa, and Akio Furusaki*
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060

(Received April 13, 1988)

Synopsis. The structure of a halochamigrene derivative, 2,10-dibromo-3-chlorochamigran-7-en-9-ol, isolated from the red alga *Laurencia* species has been determined by spectral and chemical methods as well as X-ray crystallographic analysis of the ketone derivative. Furthermore, the conformations of this compound and its derivatives are briefly discussed.

During the course of our continuing search for the constituents of the red alga *Laurencia nipponica* Yamada, we have isolated a halogenated chamigrene derivative **1** from the specimens collected at Hamamasu[2)] and other locations[3)] in Hokkaido. In this paper, we report the structural determination of this compound.

Compound **1** was analyzed for $C_{15}H_{23}OBr_2Cl$ by elemental analysis together with low and high resolution mass spectrometry. The ^1H NMR spectrum of **1** presented signals at $\delta=0.99$ (3H, s), 1.22 (3H, s), 1.70 (3H, s), and 2.05 (3H, dd, $J=1.5$, 1.5 Hz) due to four methyl groups and at $\delta=4.27$ (1H, br d, $J=9$ Hz), 4.37 (1H, d, $J=9$ Hz), 4.90 (1H, dd, $J=10$, 8 Hz), and 5.44 (1H, dddd, $J=3$, 1.5, 1.5, 1.5 Hz) due to three methine protons and an olefinic proton. Acetylation of **1** with acetic anhydride and pyridine gave the corresponding acetate **2**, $C_{17}H_{25}O_2Br_2Cl$. Double resonance experiments on the ^1H NMR spectrum of the acetate **2** indicated the presence of ■-C(CH_3)=CH-CH(OAc)-CH(Br or Cl)-■ (■; quaternary carbon) grouping in the molecule. Oxidation of **1** with Jones reagent yielded an α,β-unsaturated ketone **3**, $C_{15}H_{21}OBr_2Cl$. In view of the above-mentioned data coupled with the coexistence of **1** with many other halochamigrenes in the same alga,[2,3)] it was strongly suggested that compound **1** would be a halochamigrene derivative. Comparison of the physical properties of **1** with those of previously reported halochamigrene derivatives suggested that compound **1** is 2,10-dibromo-3-chlorochamigran-7-en-9-ol,[4)] which has been obtained as the major metabolite from *Laurencia pacifica* Kylin collected at near Ensenada, Mexico. The IR and ^1H NMR spectra of both compounds along with their derivatives were identical. The proposed structure **1** for 2,10-dibromo-3-chlorochamigran-7-en-9-ol, however, has been deduced mainly from spectral analysis.[4)] Therefore, in order to confirm the structure of **1** including the absolute configuration, a single crystal of the ketone **3** was subjected to X-ray crystallographic analysis.

The crystal data for **3** were as follows: $C_{15}H_{21}OBr_2Cl$, mol wt 412.59, monoclinic, space group $P2_1$, $a=9.773(4)$, $b=10.897(5)$, $c=7.616(2)$ Å, $\beta=92.40(3)°$, $Z=2$, $D_c=1.691$ g cm^{-3}. The structure was solved by the Monte Carlo direct method,[5)] and refined by the block-diagonal least-square method with anisotropic thermal parameters. The absolute configuration was determined by Hamilton's method;[6)] the *R*-factor ratio for the two enantiomeric structures, 1.037, excluded one of them at the 99.5% confidence level. After all the hydrogen atoms had been located in a difference Fourier map, further full-matrix least-squares refinements were carried out including the hydrogen atoms with the same fixed isotropic temperature factors of 2.5 Å^2. The final *R*-value was 0.054.[7)] The molecular framework obtained is shown

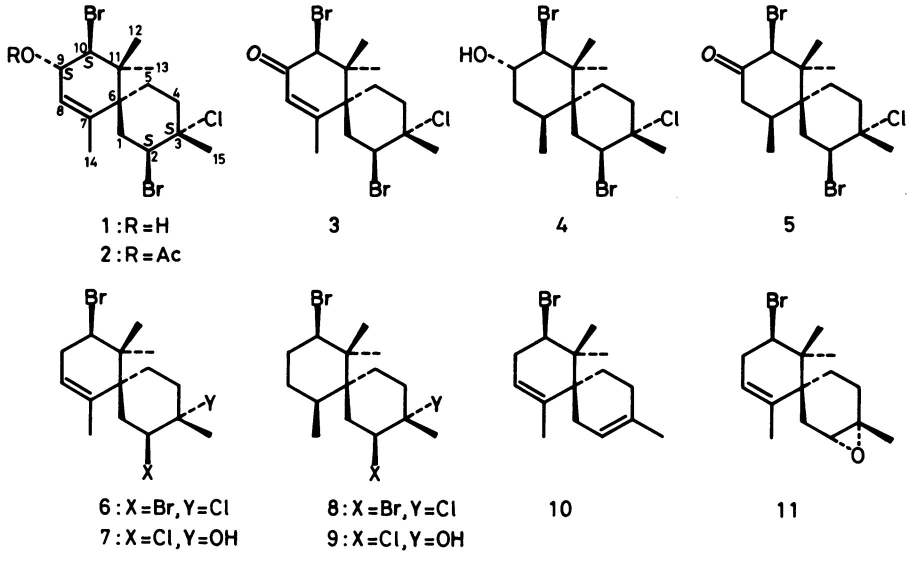


Fig. 1.

in Fig. 2. Thus, the molecular structure has been established as formula **3**.[8)]

The C-9 configuration in **1** could be established on the basis of the coupling constant of the pertinent proton at C-9 in the ^{1}H NMR spectrum of the hydrogenated product **4**.[9)] The *J*-value, J=11 Hz, between the protons at C-9 and C-10 indicated that the stereochemistry of the substituents at C-9 and C-10 is trans diequatorial to each other, thus showing that the absolute configuration at C-9 is *S*. Consequently, the absolute structure of 2,10-dibromo-3-chlorochamigran-7-en-9-ol is represented by formula **1**.

In the previous paper,[10)] we have reported that the conformations of the B-ring in the halochamigrene derivatives, such as **6** and **7**, are not chair form (formulae **6C** and **7C**) (Fig. 3) but rather twist boat form (formulae **6B** and **7B**). Compound **1**, which has the same structural feature as **6** except for the hydroxyl group at C-9, seemed to adopt a conformation, formula **1B**, very similar to those of **6** and **7** (**6B** and **7B**). In fact, in the ^{1}H NMR spectra the signals of the methyl group at C-7 in **1** and **2** were shifted downfield compared with those[10)] of compounds **10** and **11**. Furthermore, the coupling constants of the protons at C-2 in **1** and **2** indicated that these protons are neither axial nor equatorial proton on the cyclohexane ring with the normal chair conformation as observed in the case of **6** and **7**. Since the situation was almost same for the ketone **3**, the ketone **3** seemed to take conformation **3B**. However, as described above, the X-ray analysis of the ketone **3** showed that the B-ring conformation is a somewhat deformed chair form (Fig. 2). Detailed analysis of the ^{1}H NMR spectra of the ketone **3** and its dihydro derivative **5** gave the following information. In the ^{1}H NMR spectrum of **3**, some signals were rather broad at room temperature, whereas measuring at −30 °C sharpened the signals. In the spectrum measured at −30 °C, the signal due to the C_2–H was observed at δ=4.89, whose coupling constant, J=11 and 7 Hz, was compatible with those of **1** and **2**. This indicates that the ketone **3** exists in solution at room temperature as a mixture of interconverting conformers, reflecting the broad signals in the ^{1}H NMR spectrum. On the other hand, the ^{1}H NMR spectrum of **5** showed the signal due to the C_2–H at δ=4.43 (J=13 and 4 Hz), thus indicating that the B-ring conformation of the dihydro derivative **5** is represented by formula **5C** which is very similar to the conformations **8C** and **9C** of the compounds **8** and **9**.[10)] Above results suggest that, although the B-ring conformation of the ketone **3** took the chair form (**3C**) in the solid state, a preferred conformation in solution would be twist boat form (**3B**).

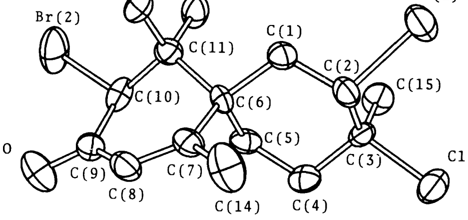


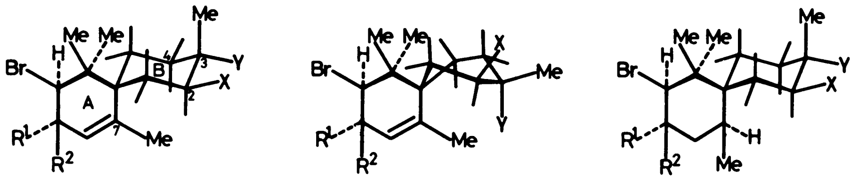
Fig. 2. A perspective view of the **3** molecule.

2,10-Dibromo-3-chlorochamigran-7-en-9-ol (**1**) is the first example of the halochamigrene derivatives from *Laurencia* species with a trans-diequatorial bromohydrin moiety at C-9 and C-10 instead of cis-bromohydrin at C-9 and C-10 which have unexceptionally been encountered in a number of halogenated chamigrane-type sesquiterpenoids.[11)]

Experimental

All the mps were uncorrecterd. The IR spectra were recorded on a JASCO A-102 spectrophotometer and the UV spectrum on a Shimadzu UV-240 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-FX 200 or a JEOL JNM-FX 100 spectrometer, using tetramethylsilane as an internal reference in $CDCl_3$. The low and high resolution mass spectra were taken at 70 eV with a JEOL JMS-D300 spectrometer. Optical rotations were determined on a JASCO DIP-140 polarimeter in $CHCl_3$. Silica gel (Merck, Kieselgel 60, 70—230 mesh) and silica gel (Merck, Kieselgel GF_{254} (Type 60)) were used for column and thin-layer chromatography, respectively.

1: Mp 119—120 °C (diisopropyl ether); $[\alpha]_D^{19}$ +25.3° (*c* 1.39); IR (Nujol), ν_{max} 3330, 1310, 1220, 1143, 1112, 1079, 1041, 1018, 999, 985, 850, and 810 cm^{-1}; ^{1}H NMR, in the text; ^{13}C NMR (25.0 MHz), δ=17.8 (q), 24.1 (q), 25.1 (q), 25.7 (q), 31.5 (t), 39.1 (t), 40.1 (t), 45.5 (s), 47.9 (s), 62.4 (d), 70.6 (s), 70.9 (d), 73.0 (d), 124.0 (d), and 143.0 (s); MS, *m/z* (rel intensity) 337, 335, 333 (0.3:0.9:0.7; M^+—Br), 319, 317, 315 (0.3:0.9:0.7; M^+—Br—H_2O), 164, 162 (3:3), 157 (2), 145 (2), 135 (3), 133 (2), 119 (23), 107 (3), 105 (4), 93 (3), 91 (5), 83 (100), 81 (2), 79 (3), 77 (3), 69 (3), 67 (2), 65 (2), 55 (5), 53 (3), 43 (2), and 41 (6). Found: *m/z* 393.9699. Calcd for



6C : R^1=R^2=H, X=Br, Y=Cl
7C : R^1=R^2=H, X=Cl, Y=OH
1C : R^1=OH, R^2=H, X=Br, Y=Cl
3C : R^1=R^2=O, X=Br, Y=Cl

6B : R^1=R^2=H, X=Br, Y=Cl
7B : R^1=R^2=H, X=Br, Y=OH
1B : R^1=OH, R^2=H, X=Br, Y=Cl
3B : R^1=R^2=O, X=Br, Y=Cl

8C : R^1=R^2=H, X=Br, Y=Cl
9C : R^1=R^2=H, X=Cl, Y=OH
4C : R^1=OH, R^2=H, X=Br, Y=Cl
5C : R^1=R^2=O, X=Br, Y=Cl

Fig. 3. B-ring conformations (H in the B-ring are omitted).

$C_{15}H_{21}{}^{79}Br^{79}Br^{35}Cl$: M−$H_2O$, 393.9699.

Found: C, 43.34; H, 5.63%. Calcd for $C_{15}H_{23}OBr_2Cl$: C, 43.45; H, 5.59%.

Acetylation of 1. Acetylation of **1** (17 mg) was carried out with acetic anhydride and pyridine by the usual method. The acetylated product was purified by column chromatography over silica gel to yield **2** (22 mg); colorless gum; $[\alpha]_D^{19}$ +75.6° (*c* 1.75); IR ($CHCl_3$), ν_{max} 1732, 1310, 1237, 1162, 1142, 1115, 1081, 1021, 991, 966, 957, 850, and 813 cm^{-1}; ^{1}H NMR, δ=1.03 (3H, s), 1.25 (3H, s), 1.71 (3H, s), 2.04 (3H, dd, *J*=1.5, 1.5 Hz), 4.42 (1H, d, *J*=9 Hz), 4.88 (1H, dd, *J*=11, 7 Hz), 5.36 (1H, dq, *J*=3, 1.5 Hz), and 5.44 (1H, ddq, *J*=9, 3, 1.5 Hz); MS, *m/z* 400, 398, 396, 394 (0.1:0.3:0.4:0.2; M^+−CH_3COOH), 378, 376, 374 (2:14:6; M^+−Br), 336, 334 332 (15:100:62; M^+−Br−CH_2CO), 119 (25), 105 (15), 91 (23), 83 (91), 55 (15), 43 (94), and 41 (24). Found: *m/z* 393.9701. Calcd for $C_{15}H_{21}{}^{79}Br^{79}Br^{35}Cl$: M−$CH_3COOH$, 393.9700.

Saponification of 2. A solution of **2** (9 mg) and potassium carbonate (15 mg) in methanol (1 ml) was stirred at room temperature for 50 min and then worked up in the usual way to give **1** (8 mg); The spectral data were identical with those of natural alcohol (**1**).

Oxidation of 1. To a solution of **1** (14 mg) in acetone (3 ml) was added Jones reagent dropwise with swirling at room temperature. After the usual work-up, the oily product was chromatographed on a silica-gel plate to give **3** (11 mg); crystals; mp 133—134 °C (diisopropyl ether); $[\alpha]_D^{17}$ −3.28° (*c* 1.54); UV (EtOH), λ_{max} 244 nm (ε 11800); IR (CCl_4), ν_{max} 1680, 1620, 1215, 1172, 1080, 970, 880, and 860 cm^{-1}; ^{1}H NMR, δ=1.02 (3H, br s), 1.35 (3H, br s), 1.74 (3H, s), 2.30 (3H, d, *J*=1.5 Hz), 4.85 (1H, m), 4.93 (1H, br s), and 6.01 (1H, br s); ^{1}H NMR (100 MHz, at −30 °C), δ=1.02 (3H, s), 1.37 (3H, s), 1.75 (3H, s), 2.34 (3H, br s), 4.89 (1H, dd, *J*=11, 7 Hz), 5.00 (1H, s), and 6.05 (1H, br s); MS, *m/z* 416, 414, 412, 410 (0.02:0.09:0.12:0.06; M^+), 335, 333, 331 (1:9:4; M^+−Br), 280 (13), 278 (76), 276 (60), 199 (28), 197 (100), 161 (58), 119 (12), 105 (16), 91 (31), 83 (19), 79 (14), 77 (18), 69 (18), 55 (33), 53 (27), 41 (27), and 39 (23). Found: *m/z* 409.9646. Calcd for $C_{15}H_{21}O^{79}Br^{79}Br^{35}Cl$: M, 409.9652.

Hydrogenation of 1. Hydrogenation of **1** (8 mg) was performed in ethyl acetate over PtO_2-catalyst. After the usual work-up, the residual oil was chromatographed on a silica-gel plate to afford **4** (7 mg); colorless oil; $[\alpha]_D^{19}$ +46.3° (*c* 0.72); IR ($CHCl_3$), ν_{max} 3550, 1300, 1120, 1095, 1047, 905, 890, 880, 873, 861, 838, and 810 cm^{-1}; ^{1}H NMR, δ=1.10 (3H, s), 1.16 (3H, s), 1.22 (3H, d, *J*=7.5 Hz), 1.71 (3H, s), 3.93 (1H, ddd, *J*=11, 11, 5 Hz), 4.17 (1H, d, *J*=11 Hz), and 4.41 (1H, dd, *J*=13, 4 Hz); MS, *m/z* 339, 337, 335 (1:5:4; M^+−Br), 321, 319, 317 (2:7:5; M^+−Br−H_2O), 149 (7), 121 (7), 109 (6), 105 (7), 93 (9), 91 (9), 85 (100), 83 (7), 81 (7), 79 (6), 77 (6), 69 (6), 67 (7), 57 (8), 55 (25), 53 (6), 43 (9), and 41 (40). Found: *m/z* 335.0776. Calcd for $C_{15}H_{25}O^{79}Br^{35}Cl$: M−Br, 335.0776.

Oxidation of 4. Oxidation of **4** (10 mg) was carried out with Jones reagent in acetone in the usual manner to give **5** (9 mg); crystals; mp 181—183 °C (diisopropyl ether); IR ($CHCl_3$), ν_{max} 1730, 1305, 1280, 1147, 1095, 867, and 859 cm^{-1}; ^{1}H NMR, δ=1.05 (3H, s), 1.16 (3H, d, *J*=7 Hz), 1.23 (3H, s), 1.75 (3H, s), 4.43 (1H, dd, *J*=13, 4 Hz), and 4.81 (1H, s); MS, *m/z* 337, 335, 333 (1:5:4; M^+−Br), 121 (14), 119 (55), 105 (9), 93 (13), 91 (13), 87 (11), 83 (100), 79 (12), 77 (11), 69 (12), 67 (10), 55 (30), 53 (19), 45 (13), 43 (9), 41 (36), and 39 (16). Found: *m/z* 333.0619. Calcd for $C_{15}H_{23}O^{79}Br^{35}Cl$: M−Br, 333.0620.

X-Ray Experiment. A single crystal with dimensions of ca. 0.2×0.3×0.5 mm^3 was used for the X-ray measurement. The cell dimensions and diffraction intensities were measured on a Rigaku four-circle diffractometer at the High Brilliance X-Ray Diffraction Laboratory of Hokkaido University, using graphite-monochromated Mo *K*α radiation (λ=0.71073 Å). The θ–2θ scan technique was applied at a θ scan speed of 4° min^{-1}; the background was counted for 10 s at each end of the scan range. The intensities of three standard reflections, measured at intervals of every 100 reflections, decreased gradually during the course of data collection; the final-intensity/initial-intensity ratios were ca. 0.988—0.994. The intensities were corrected for this damage to the sample as well as for the Lorentz and polarization factors, but not for the absorption or the extinction effect. In the range of 2θ values up to 50°, 1274 independent structure factors above the 3σ(F) level were selected for the structure determination.

We are grateful to Professor William Fenical, University of California, Scripps Institution of Oceanography, for providing us with copies of the IR and ^{1}H NMR spectra of 2,10-dibromo-3-chlorochamigran-7-en-9-ol and its derivatives; the acetate, the ketone, and the dihydro derivative.

References

1) Part 73 of "Constituents of Marine Plants". Part 72; M. Suzuki, E. Kurosawa, M. Ikura, and K. Hikichi, *Phytochemistry,* in preparation.

2) H. Kikuchi, T. Suzuki, M. Suzuki, and E. Kurosawa, *Bull. Chem. Soc. Jpn.,* **58**, 2437 (1985).

3) Unpublished result.

4) W. Fenical, *Phytochemistry,* **15**, 511 (1976).

5) A. Furusaki, *Acta Crystallogr., Sect. A,* **35**, 220 (1979).

6) W. C. Hamilton, *Acta Crystallogr.,* **18**, 502 (1965).

7) The calculations for the X-ray study were performed on a HITAC M-280H computer at the Hokkaido University Computing Center, using our own programs.

8) The tables of the atomic parameters and bond distances and angles and the F_o−F_c table are kept at the Chemical Society Japan (Document No. 8823).

9) Oxidation of 2,10-dibromo-3-chlorochamigran-7-ene (**6**) with *m*-chloroperbenzoic acid gave the α-epoxide.[12,13] If hydrogenation follows the same course (attack from the less-hindered α-side) as oxidation, the secondary methyl group at C-7 of the hydrogenated product must be β-configuration.

10) M. Suzuki, A. Furusaki, and E. Kurosawa, *Tetrahedron,* **35**, 823 (1979).

11) "Marine Natural Products," ed by P. J. Scheuer, Academic Press, New York; J. D. Martin and J. Darias, (1978), Vol. 1, pp. 138—152; K. L. Erickson, (1983), Vol. 5, pp. 164—173.

12) B. M. Howard and W. Fenical, *Tetrahedron Lett.,* **1975**, 1687; M. Ojika, Y. Shizuri, and K. Yamada, *Phytochemistry,* **21**, 2410 (1982); T. Suzuki, H. Kikuchi, and E. Kurosawa, *Bull. Chem. Soc. Jpn.,* **55**, 1561 (1982).

13) A. Furusaki, C. Katayama, T. Matsumoto, M. Suzuki, T. Suzuki, H. Kikuchi, and E. Kurosawa, *Bull. Chem. Soc. Jpn.,* **55**, 3398 (1982).