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# THE ABSOLUTE CONFIGURATIONS OF HALOGENATED CHAMIGRENE DERIVATIVES FROM THE MARINE ALGA, *LAURENCIA GLANDULIFERA* KÜTZING[1]

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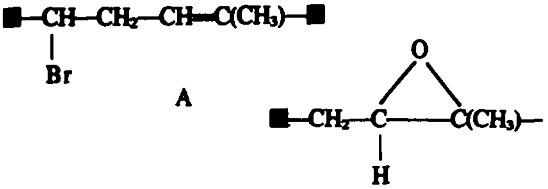
**Abstract**—The absolute configurations of halogenated chamigrene derivatives, isolated from *L. glandulifera* Kützing, 10-bromo-3,4-epoxy-α-chamigrene (1), glanduliferol (2), 10-bromo-α-chamigren-4-one (3), 4,10-dibromo-3-chloro-α-chamigrene (4) and 10-bromo-α-chamigrene (5), have been determined by X-ray diffraction analysis of 1 and subsequently, by relating 2, 3, 4 and 5 to 1 with the chemical methods. In addition, the absolute configuration of (−)-α-chamigrene (6), yielded on the process of the above chemical transformation, has been elucidated.

Many halogenated chamigrene derivatives have been isolated from the marine algae genus *Laurencia* (Rhodomelaceae; Rhodophyta).[2-7] In the course of our continued studies of chamigrene derivatives, we have reported the structures of four chamigrene-type bromosesquiterpenes, isolated from *L. glandulifera* Kützing, 10 - bromo - 3,4 - epoxy - α - chamigrene (1), glanduliferol (2), 10 - bromo - α - chamigren - 4 - one (3) and 10 - bromo - β - chamigren - 4 - one.[7a,7b] Furthermore, an extensive study of the hydrocarbon part of the neutral essential oil of this alga led to the isolation of 4,10 - dibromo - 3 - chloro - α - chamigrene (4) and 10 - bromo - α - chamigrene (5), previously isolated from *L. pacifica* and *L.* species, collected at the Gulf of California.[7c,7d] We have elucidated the absolute configurations of 1, 2, 3, 4 and 5 by X-ray diffraction analysis and the chemical methods. The present paper describes the isolation, the structures and the stereochemistry of these halogenated chamigrenes in detail.

### *Structure of* 10-*bromo*-3,4-*epoxy*-α-*chamigrene* (1)[7a]

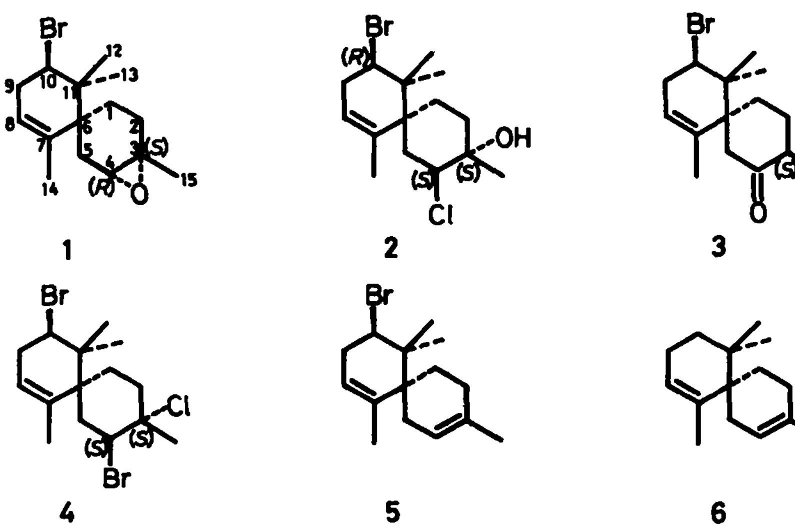
10-Bromo-3,4-epoxy-α-chamigrene, $C_{15}H_{23}OBr$, ($M^+$ 300 and 298), m.p. 53–54°, $[\alpha]_D -92°$, shows no OH nor CO groups in its IR spectrum and thus, it is suggested that the O moiety is involved in an ether link. The PMR and the spin decoupling studies indicated the presence of an ABXY pattern [δ 5.03 (1 H, m, X of an ABXY), 4.52 (1 H, dd, J = 8.0, 8.0 Hz, Y of an ABXY) and an AB part of an ABXY centred at 2.5 (2 H, m)] and an ABX pattern [2.84 (1 H, dd, J = 2.0, 2.0, X of an ABX) and an AB part of an ABX centred at 1.98 and 2.10 (each 1 H, dd, J = 16.0, 2.0)]. In up-field region appear signals for Me groups at 0.93 and 1.10 (each 3 H, s, probably *gem*-dimethyl), 1.25 (3 H, s, epoxide Me) and 1.74 (3 H, br. s, olefinic Me). The above-mentioned PMR and the spin decoupling studies indicated the presence of the following partial structures A and B in 1.



$$■\!-\!\underset{\displaystyle Br}{\underset{|}{CH}}\!-\!CH_2\!-\!CH\!=\!C(CH_3)\!-\!■$$

A

B



1 2 3

4 5 6

Fig. 1.

In view of the above-mentioned PMR and the spin decoupling studies, the transformation of 1 to a conjugated cyclohexadiene[7a] [$C_{15}H_{22}O$, $\lambda_{max}^{EtOH}$ 264 nm ($\epsilon$ 2900)] and also the biogenetical considerations, the structure of 1 would be represented as 10 - bromo - 3,4 - epoxy - α - chamigrene and this was further supported by the mass and $^{13}C$ NMR spectra. The main fragmentations of the mass spectrum are reasonably explicable by the following Scheme 1 and the $^{13}C$ NMR spectrum (Table 1) is completely in conformity with the structure of 1.

Table 1. $^{13}C$ NMR spectrum of 1

| δ | Multiplicity | Assignment |
|---|---|---|
| 141.6 | s | C-7 |
| 119.2 | d | C-8 |
| 61.9 | d | C-10 |
| 58.7 | d | C-4 |
| 55.5 | s | C-3 |
| 43.0 | s | C-6 and 11 |
| 42.5 | s | |
| 35.7 | t | C-1, 2, 5, and 9 |
| 29.4 | t | |
| 27.8 | t | |
| 26.5 | t | |
| 25.4 | q | C-14 |
| 22.3 | q | C-15 |
| 20.6 | q | C-12 and 13 |
| 17.9 | q | |

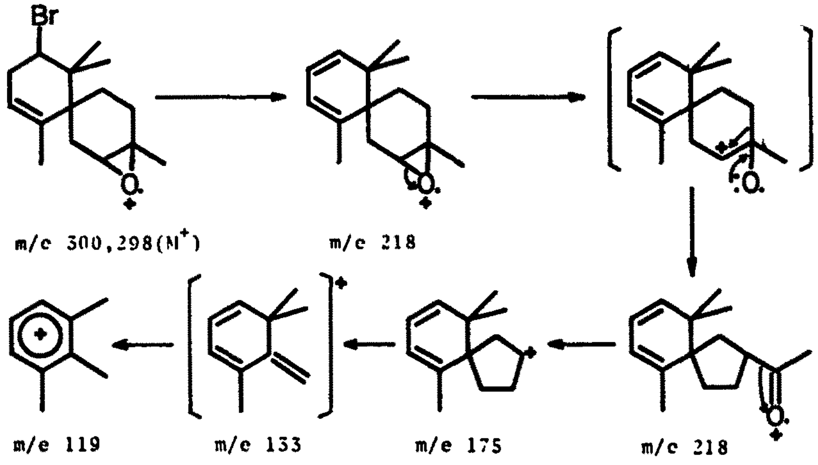
In order to elucidate the structure of 1 containing the absolute configuration, a single crystal of 1 was subjected to X-ray diffraction analysis.

Colorless, platelike crystals of 1 were obtained by cooling a hot methanol solution to room temperature. A single crystal with dimensions of about 0.4 × 0.4 × 0.2 mm was used for the X-ray measurement. Cell dimensions and reflection intensities were measured on a Rigaku four-circle diffractometer using CuKα radiation (λ = 1.54178 Å) monochromatized with a LiF crystal. The intensity measurement was made by the θ-2θ continuous-scan technique at a scan rate of about 1°(θ)/min; the background was measured for 20-30 s at each end of the scan range. The intensities were corrected for the Lorentz and polarization factors, but not for either the absorption or the extinction effect. In the range of 2θ values up to 140°, 1507 structure factor magnitudes above $2\sigma(F_0)$ were selected for the subsequent structure analysis and refinement.

Crystal data: $C_{15}H_{23}OBr$, mol. wt. = 299.3, orthorhombic, a = 11.862(5), b = 15.210(6), c = 7.961(4) Å, Z = 4, $D_x$ = 1.384 gcm$^{-3}$, F(000) = 624, $\mu$(CuKα) = 37.7 cm$^{-1}$. Systematic absences, h00 for h odd, 0k0 for k odd, 00l for l odd; space group $P2_12_12_1$($D_2^4$, No. 19).

The structure was solved by the heavy-atom method. Approximate coordinates of all non-H atoms were refined by the block-diagonal-matrix least-squares method, at first with isotropic and then with anisotropic thermal parameters. The value of the conventional agreement factor, $R = \Sigma||F_0| - |F_c||/\Sigma|F_0|$, dropped to 9.4%.

At this stage of the refinement, the absolute configuration was determined by taking account of the anomalous scattering of bromine for CuKα radiation. The observed and calculated Bijvoet inequalities for twenty pairs of reflections clearly indicated that the actual absolute configuration corresponds to that shown in Fig. 2. This



Scheme 1.

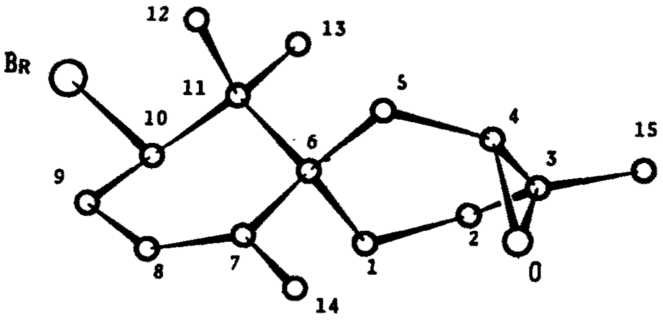


Fig. 2. Molecular configuration viewed along the crystallographic a axis

Table 2. Atomic fractional coordinates (Br, O, C, $\times 10^4$; H, $\times 10^3$) and thermal parameters (Br, O, C, $\times 10^4$), with least-squares standard deviations in parentheses

(a) non-hydrogen atoms

| Atom | x | y | z | $\beta_{11}$ | $\beta_{22}$ | $\beta_{33}$ | $\beta_{12}$ | $\beta_{13}$ | $\beta_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| Br | -1776(1) | 1878(1) | 201(1) | 103(1) | 68(0) | 270(1) | 16(1) | -73(2) | 66(1) |
| O | 1225(4) | -153(4) | 7299(6) | 75(3) | 66(2) | 163(7) | -11(5) | -57(8) | -20(7) |
| C(1) | -363(5) | 874(4) | 5615(8) | 73(4) | 48(2) | 155(9) | 18(5) | 50(10) | -20(8) |
| C(2) | -759(5) | 16(6) | 6396(9) | 64(4) | 71(4) | 161(9) | -32(6) | 22(10) | 4(10) |
| C(3) | 195(6) | -607(5) | 6791(9) | 79(4) | 55(3) | 167(9) | -29(6) | -26(11) | 12(9) |
| C(4) | 1168(5) | -581(4) | 5651(8) | 69(4) | 44(2) | 179(10) | -3(5) | -44(10) | -18(8) |
| C(5) | 1173(4) | -26(4) | 4095(8) | 56(3) | 39(2) | 169(8) | 6(4) | 17(9) | -18(7) |
| C(6) | 432(4) | 827(3) | 4064(7) | 55(3) | 32(2) | 148(7) | 1(4) | 13(8) | -29(6) |
| C(7) | 1215(5) | 1637(4) | 4199(9) | 68(4) | 40(2) | 196(10) | -17(5) | 11(10) | -52(8) |
| C(8) | 1051(8) | 2361(5) | 3313(14) | 112(6) | 37(2) | 306(17) | -41(7) | -6(17) | -19(11) |
| C(9) | 145(9) | 2493(5) | 2039(14) | 136(8) | 39(2) | 309(19) | -21(7) | -37(21) | 28(12) |
| C(10) | -725(6) | 1771(4) | 2146(9) | 83(4) | 41(2) | 202(10) | 9(5) | 8(11) | 6(8) |
| C(11) | -219(4) | 853(3) | 2319(7) | 56(3) | 35(2) | 165(8) | -6(4) | -7(9) | -21(7) |
| C(12) | 590(6) | 684(5) | 841(9) | 81(4) | 65(3) | 153(9) | 18(6) | 10(11) | -35(9) |
| C(13) | -1153(6) | 147(4) | 2290(10) | 75(4) | 48(3) | 215(11) | -27(6) | -64(12) | 3(9) |
| C(14) | 2148(7) | 1609(6) | 5456(12) | 98(5) | 64(3) | 237(14) | -47(7) | -40(14) | -56(12) |
| C(15) | -83(10) | -1411(7) | 7776(12) | 138(8) | 74(4) | 201(14) | -51(10) | 8(18) | 36(13) |

(b) hydrogen atoms

| Atom | x | y | z | B | Atom | x | y | z | B |
|---|---|---|---|---|---|---|---|---|---|
| H(1a) | -106(9) | 120(7) | 529(16) | 6(2) | H(12b) | 137(9) | 114(7) | 102(15) | 6(2) |
| H(1b) | 2(9) | 119(7) | 634(14) | 5(2) | H(12c) | 30(9) | 86(7) | 39(15) | 6(2) |
| H(2a) | -128(6) | -34(5) | 581(10) | 3(1) | H(13a) | -109(9) | -54(7) | 238(14) | 5(2) |
| H(2b) | -125(11) | 15(8) | 744(17) | 7(2) | H(13b) | -159(9) | 18(7) | 83(14) | 5(2) |
| H(4) | 155(9) | -126(7) | 525(15) | 6(2) | H(13c) | -156(11) | 14(8) | 290(17) | 7(2) |
| H(5a) | 73(6) | -46(5) | 304(10) | 4(1) | H(14a) | 201(9) | 155(7) | 616(14) | 6(2) |
| H(5b) | 189(8) | 14(6) | 383(11) | 4(2) | H(14b) | 242(10) | 210(8) | 532(17) | 7(2) |
| H(8) | 148(9) | 290(7) | 339(14) | 6(2) | H(14c) | 263(9) | 115(7) | 511(16) | 6(2) |
| H(9a) | 40(12) | 241(9) | 113(18) | 7(3) | H(15a) | 67(15) | -178(13) | 801(24) | 10(4) |
| H(9b) | -33(14) | 310(12) | 213(23) | 10(4) | H(15b) | -66(12) | -171(10) | 724(20) | 8(3) |
| H(10) | -108(9) | 189(7) | 295(13) | 5(2) | H(15c) | -35(8) | -129(6) | 848(13) | 5(2) |
| H(12a) | 70(7) | 8(6) | 88(12) | 4(2) | | | | | |

Table 3. Bond distances (Å) and angles (deg.); least-squares estimated standard deviations are given in parentheses

| | | | | | |
|---|---|---|---|---|---|
| C(1)-C(2) | 1.520(10) | C(2)-C(1)-C(6) | 118.2(5) | C(6)-C(7)-C(14) | 118.0(6) |
| C(1)-C(6) | 1.556(8) | C(1)-C(2)-C(3) | 113.1(5) | C(8)-C(7)-C(14) | 119.4(7) |
| C(2)-C(3) | 1.508(10) | C(2)-C(3)-C(4) | 116.3(6) | C(7)-C(8)-C(9) | 125.5(7) |
| C(3)-C(4) | 1.468(9) | C(2)-C(3)-C(15) | 117.3(7) | C(8)-C(9)-C(10) | 110.9(7) |
| C(3)-C(15) | 1.489(13) | C(2)-C(3)-O | 112.8(6) | C(9)-C(10)-C(11) | 113.7(6) |
| C(3)-O | 1.462(9) | C(4)-C(3)-C(15) | 121.5(7) | C(9)-C(10)-Br | 108.9(6) |
| C(4)-C(5) | 1.499(9) | C(4)-C(3)-O | 60.1(4) | C(11)-C(10)-Br | 113.0(4) |
| C(4)-O | 1.466(8) | C(15)-C(3)-O | 115.3(7) | C(6)-C(11)-C(10) | 107.0(5) |
| C(5)-C(6) | 1.567(7) | C(3)-C(4)-C(5) | 122.0(5) | C(6)-C(11)-C(12) | 111.2(4) |
| C(6)-C(7) | 1.547(8) | C(3)-C(4)-O | 59.7(4) | C(6)-C(11)-C(13) | 110.1(5) |
| C(6)-C(11) | 1.590(8) | C(5)-C(4)-O | 119.3(5) | C(10)-C(11)-C(12) | 109.3(5) |
| C(7)-C(8) | 1.322(10) | C(4)-C(5)-C(6) | 118.5(5) | C(10)-C(11)-C(13) | 110.7(5) |
| C(7)-C(14) | 1.493(11) | C(1)-C(6)-C(5) | 111.5(4) | C(12)-C(11)-C(13) | 108.6(5) |
| C(8)-C(9) | 1.492(15) | C(1)-C(6)-C(7) | 105.8(5) | | |
| C(9)-C(10) | 1.509(11) | C(1)-C(6)-C(11) | 113.5(4) | | |
| C(10)-C(11) | 1.526(8) | C(5)-C(6)-C(7) | 108.7(4) | | |
| C(10)-Br | 1.994(7) | C(5)-C(6)-C(11) | 107.9(4) | | |
| C(11)-C(12) | 1.540(9) | C(7)-C(6)-C(11) | 109.4(4) | | |
| C(11)-C(13) | 1.543(8) | C(6)-C(7)-C(8) | 122.6(6) | | |

assignment was supported also by the comparison of values of $R' = [\Sigma(|F_o| - |F_c|)^2/\Sigma|F_o|^2]^{1/2}$ for all the reflections used in the structure determination. Several cycles of the least-squares refinement including the anomalous scattering effect of the Br atom gave R' values of 11.18 and 11.48% to the structure depicted in Fig. 2 and its antipode, respectively. Consequently, Hamilton's test[8] rejected the latter at the 99.5% confidence level.

A difference Fourier map revealed the locations of all H atoms. The least-squares refinement was further repeated including these H atoms with isotropic temperature factors. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/[\sigma(F_o)^2 \exp(AX^2 + BY^2 + CXY + DX + EY)]$, where $X = |F_o|$ and $Y = \sin\theta/\lambda$. The intensity data were grouped with constant intervals along two coordinates, X and Y. The coefficients, A, B, C, D and E, were determined by the least-squares fit so as to give as equal values of $\langle w|\Delta F|^2\rangle$ for all the groups as possible. The final R value was 7.5%.

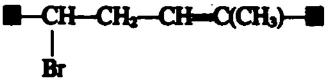
All calculations were performed on a FACOM 230-75 computer at the Computing Center of Hokkaido University, using our own programs. The atomic scattering factors were taken from International Tables.[9]

The results are given in Tables 2–4 and Fig. 2. The H atoms are denoted by the number of the C atom to which they are attached, suffixed by a, b, c, where necessary. The anisotropic and isotropic thermal parameters are defined by the equations, $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$ and $\exp[-B(\sin\theta/\lambda)^2]$, respectively.

The bond distances and angles are all within the observed range.[10] The cyclohexene ring takes a distorted half-chair conformation with the C(10) and C(11) atoms lying 0.259 and 0.518 Å, above and below the best plane through the C(6), C(7), C(8) and C(9) atoms; the Br, C(5) and C(13) atoms are equatorially or pseudo-equatorially bonded to this ring. On the other hand, the cyclohexane ring adopts a somewhat flattened, twist-boat conformation with an approximate two-fold rotation axis running through the middle points of the C(1)–C(2) and C(4)–C(5) bonds. The epoxy O atom is very close to the C(1) atom, their distance being 2.790 Å.

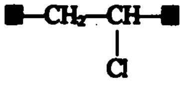
### *Structure of glanduliferol* (2)[7b]

Glanduliferol, $C_{15}H_{24}OBrCl$, ($M^+$ 336 and 334), colorless gum, $[\alpha]_D - 21.7°$, $\nu_{max}$ 3580, 1655, 1400, 1390, 1342, 1130, 1105, 1070, 1045, 990, 980, 928 and 832 cm$^{-1}$, is an alcoholic compound and furthermore, OH group should be tertiary by its resistance to acetylation with acetic anhydride in pyridine. The PMR spectrum showed the presence of four Me groups at δ 0.96, 1.22, 1.30 (each 3 H, s) and 2.0 (3 H, br. s), two two-proton signals at 2.17 (2 H, d, J = 9.5 Hz) and *ca.* 2.5 (2 H, m), 4.47 (1 H, dd, J = 10.0, 7.0, –C$\underline{H}$Br–), 4.67 (1 H, dd, J = 9.5, 9.5, –C$\underline{H}$Cl–) and 5.2 (1 H, m, olefinic proton). The spin decoupling studies provided the additional information on the structure, which indicated the presence of partial structures C and D as follows:



$$\blacksquare\!-\!\underset{\displaystyle Br}{\underset{|}{CH}}\!-\!CH_2\!-\!CH\!=\!C(CH_3)\!-\!\blacksquare$$

C



$$\blacksquare\!-\!CH_2\!-\!\underset{\displaystyle Cl}{\underset{|}{CH}}\!-\!\blacksquare$$

D

In view of $^{13}$C NMR study (Table 5), the structure of 2 would be represented as 10 - bromo - 4 - chloro - 3 - hydroxy - α - chamigrene and it was definitely confirmed by the treatment of 2 with potassium hydroxide.

Table 5. $^{13}$C NMR spectrum of 2

| δ | Multiplicity | Assignment |
|---|---|---|
| 139.9 | s | C-7 |
| 122.0 | d | C-8 |
| 71.9 | s | C-3 |
| 66.1 | d | C-4 |
| 61.2 | d | C-10 |
| 48.1 | s | C-6 |
| 42.7 | s | C-11 |
| 39.1 | t | C-1, 2, 5, and 9 |
| 36.2 | t | |
| 35.9 | t | |
| 31.6 | t | |
| 25.8 | q | C-14 |
| 24.7 | q | C-15 |
| 22.1 | q | C-12 and 13 |
| 17.3 | q | |

Table 4. Dihedral angle (deg.); the A-B-C-D angle is positive if, when looking along B to C, A has to be rotated clockwise to eclipse D

| | | | |
|---|---|---|---|
| C(6)-C(1)-C(2)-C(3) | 51.6 | C(11)-C(6)-C(7)-C(8) | 21.9 |
| C(1)-C(-)-C(3)-C(4) | -32.8 | C(11)-C(6)-C(7)-C(14) | -161.6 |
| C(1)-C(2)-C(3)-C(15) | 171.6 | C(1)-C(6)-C(11)-C(10) | 68.1 |
| C(1)-C(2)-C(3)-O | 33.9 | C(5)-C(6)-C(11)-C(10) | -167.8 |
| C(2)-C(3)-C(4)-C(5) | -5.3 | C(7)-C(6)-C(11)-C(10) | -49.7 |
| C(15)-C(3)-C(4)-C(5) | 149.3 | C(7)-C(6)-C(11)-C(12) | 69.6 |
| O-C(3)-C(4)-C(5) | -107.7 | C(7)-C(6)-C(11)-C(13) | -170.0 |
| C(2)-C(3)-O-C(4) | -108.3 | C(6)-C(7)-C(8)-C(9) | -2.5 |
| C(15)-C(3)-O-C(4) | 113.2 | C(14)-C(7)-C(8)-C(9) | -178.9 |
| C(3)-C(4)-C(5)-C(6) | 27.6 | C(7)-C(8)-C(9)-C(10) | 12.4 |
| O-C(4)-C(5)-C(6) | -43.1 | C(8)-C(9)-C(10)-C(11) | -44.4 |
| C(5)-C(4)-O-C(3) | 112.1 | C(8)-C(9)-C(10)-Br | -171.3 |
| C(4)-C(5)-C(6)-C(1) | -9.4 | C(9)-C(10)-C(11)-C(6) | 64.2 |
| C(4)-C(5)-C(6)-C(7) | 106.8 | C(9)-C(10)-C(11)-C(12) | -56.3 |
| C(4)-C(5)-C(6)-C(11) | -134.7 | C(9)-C(10)-C(11)-C(13) | -175.9 |
| C(1)-C(6)-C(7)-C(8) | -100.7 | Br-C(10)-C(11)-C(6) | -171.1 |
| C(5)-C(6)-C(7)-C(8) | 139.5 | | |

The mild treatment of **2** with 5% methanolic potassium hydroxide gave a dehydrochlorination product, $C_{15}H_{23}OBr$, which was identical with 10 - bromo - 3,4 - epoxy - α - chamigrene (**1**) by the mixed m.p. and by a comparison of the IR and PMR spectra and the optical rotation with those of an authentic specimen. This easy epoxide formation suggests that the vicinal Cl and OH groups should be *trans* as shown in Fig. 1 and easily become in the situation of anti-relationship each other, when they do react.

On the consideration of ring conformation of **2**, the PMR spectrum has given the information. The PMR spectrum of **2** showed the chloromethine proton at 4.67 (dd, J = 9.5, 9.5), coupling with the adjacent methylene protons. This coupling constant are consistent with the twist ring form, in which the dihedral angle between the chloromethine proton at C-4 and one of the adjacent methylene protons at C-5 is very small and that between the proton at C-4 and the other of methylene protons is around 140°.[11] In an attempt to clarify the configuration of the Cl and the OH groups and the ring conformation of B-ring, we studied the PMR spectrum of **2** in the presence of shift reagent, $Eu(fod)_3$ (Tables 6 and 7).

The shift reagent studies indicate that the stereochemistry of the Cl is equatorial since the chloromethine proton clearly gives the typical coupling constant for axial H (dd, J = 12.0, 5.0). In addition, the equatorial nature of the OH group is indicated by the less induced shifts for the axial protons at C-1 and C-5 than those at C-2 and C-4 and also by the equal induced shifts for both axial and equatorial protons at C-1 and C-5.[12]

The stereochemistry of B-ring in **2** is now shown provisionally as the formula **7** (Fig. 3). The alternative formula **8** seems to be energetically unfavorable, since one Me group of *gem*-dimethyl group at C-11 has equatorial configuration and thus non-bonded interaction of the equatorial Me group at C-11 to the Cl at C-4 are recognized on the Dreiding model. On the other hand, it is apparent that the shape of B-ring in formula **7** fundamentally changes in twist boat form to relieve the interaction between the Me group at C-7 and two axial hydrogens at C-2 and C-4. Formula **9**, which possess the twist boat form for B-ring, is now proposed for glanduliferol (**2**), decreasing the interaction between the Me group at C-7 and two axial hydrogens at C-2 and C-4 in **7** and permitting the coupling constant (J = 9.5, 9.5) for the chloromethine proton at C-4 coupled to the adjacent methylene group at C-5. From these considerations, it is assumed that the conformation of B-ring in **2** changes to normal chair form from twist-boat form during the addition of shift reagent of $Eu(fod)_3$, because of newly generated non-bonded interaction of $Eu(fod)_3$-complex, and thus the change of coupling constant of the chloromethine proton, J = 9.5, 9.5 → 12.0, 5.0 (on addition of the shift reagent), is smoothly explained.

Moreover, in the PMR spectrum of **2**, the signal of the olefinic Me at C-7 appears in considerably low field compared with those of the other compounds, **1**, **3** and **5** (Table 8). This down field shift is easily explicable by the reason that the olefinic Me at C-7 is in the situation closed to the OH group in formula **9**. This assumption is supported by the hydrogenation of **2** with $PtO_2$ yielding the dihydro compound (**10**). In the PMR spectrum of **10**, the coupling constant (dd, J = 11.0, 5.0) of the chloromethine proton at C-4 reveals that the Cl has an equatorial orientation and the change of coupling constant (9.5, 9.5 on **2** → 11.0, 5.0 on **10**) seems to be caused by the change of B-ring conformation from twist boat form (formula **9**) to normal chair form (formula **10**) which should be accompanied by the change of A-ring shape from slightly distorted chair form to normal chair form during the hydrogenation of **2**, and disappearance of one of the two interactions between the Me group at C-7 and two hydrogens at C-2 and C-4 in **7**.

### *Structure of 10-bromo-α-chamigren-4-one* (**3**)[7a]

10-Bromo-α-chamigren-4-one, $C_{15}H_{23}OBr$, ($M^+$ 300 and 298), m.p. 78–79°, $[\alpha]_D - 88°$, showed the presence of

Table 6. Spin decoupling results in the PMR spectra of **2** in $CCl_4$ after the addition of 0.5 molar equivalents of $Eu(fod)_3$

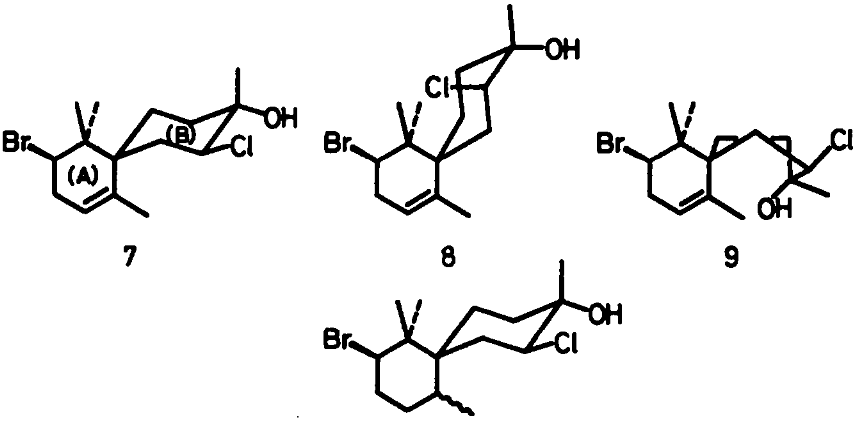
| Run | Proton (δ) | | | | Multiplicity change | Splitting decoupled (Hz) |
|---|---|---|---|---|---|---|
| | Irradiated | | Observed | | | |
| 1a | $C_4$-H | 13.74 | $C_5$-H(ax) | 6.15 | dd(J=14,12) → dd(?) | |
| b | | | $C_5$-H(eq) | 5.07 | dd(J=14,5) → d(J=14) | 5 |
| 2a | $C_5$-H(ax) | 6.15 | $C_4$-H | 13.74 | dd(J=12,5) → br s | 12 |
| b | | | $C_5$-H(eq) | 5.07 | dd(J=14,5) → br s | 14 |
| 3a | $C_5$-H(eq) | 5.07 | $C_4$-H | 13.74 | dd(J=12,5) → d(J=12) | 5 |
| b | | | $C_5$-H(ax) | 6.15 | dd(J=14,12) → br d(J=12) | 14 |
| 4a | $C_2$-H(ax) | 10.90 | $C_2$-H(eq) | 9.80 | br d(J=14) → br s | 14 |
| b | | | $C_1$-H(ax) | $\sim$5.4 | ch | |
| 5a | $C_2$-H(eq) | 9.80 | $C_2$-H(ax) | 10.90 | br t($W_H$ 33) → dd(J=12,4) | 14 |
| b | | | $C_1$-H(ax) | $\sim$5.4 | ch | |
| 6a | $C_1$-H(ax) | $\sim$5.4 | $C_2$-H(ax) | 10.90 | br t($W_H$ 33) → m($W_H$ 24) | |
| b | | | $C_2$-H(eq) | 9.80 | br d(J=14, $W_H$ 24) → br d(J=14, $W_H$ 20) | |

Abbreviations; "s": singlet, "d": doublet, "t": triplet, "dd": double doublet.
"m": multiplet, "ch": change, "br": broad

Table 7. Chemical shifts (δ, ppm) and $\Delta_{Eu}$-values (ppm) in the PMR spectra of 2 in $CCl_4$ containing various amounts of $Eu(fod)_3$

| $Eu(fod)_3$ | 0 | 0.25 mole | | 0.5 mole | | 1.0 mole | |
|---|---|---|---|---|---|---|---|
| Proton | δ | δ | $\Delta^{0.25}_{Eu}$ | δ | $\Delta^{0.5}_{Eu}$ | δ | $\Delta^{1.0}_{Eu}$ |
| $C_1$-C$\underline{H}$(ax) | 1.6 ∼ 1.9 | ∼3.7 | -1.8 ∼ -2.1 | ∼5.4 | -3.5 ∼ -3.8 | ∼7.3 | -5.4 ∼ -5.7 |
| $C_1$-C$\underline{H}$(eq) | | ∼2.9 | -1.0 ∼ -1.3 | ∼3.8 | -1.9 ∼ -2.2 | ∼5.1 | -3.2 ∼ -3.5 |
| $C_2$-C$\underline{H}$(ax) | | 6.30 | -4.4 ∼ -4.7 | 10.90 | -9.0 ∼ -9.3 | 14.60 | -12.7 ∼ -13.0 |
| $C_2$-C$\underline{H}$(eq) | | 5.80 | -3.9 ∼ -4.2 | 9.80 | -7.9 ∼ -8.2 | 16.20 | -14.3 ∼ -14.6 |
| $C_3$-C$\underline{H}_3$ | 2.30 | 4.74 | -2.44 | 7.95 | -5.65 | 11.40 | -9.10 |
| $C_4$-C$\underline{H}$ | 4.67 | 9.32 | -4.65 | 13.74 | -9.07 | 18.68 | -14.01 |
| $C_5$-C$\underline{H}$(ax) | 2.20 | 4.21 | -2.01 | 6.15 | -3.95 | 8.19 | -5.99 |
| $C_5$-C$\underline{H}$(eq) | 2.20 | ∼3.7 | -1.5 | 5.07 | -2.87 | 6.65 | -4.45 |
| $C_7$-C$\underline{H}_3$ | 2.00 | 2.92 | -0.92 | 3.79 | -1.79 | 4.79 | -2.79 |
| $C_8$-C$\underline{H}$ | 5.20 | 5.51 | -0.31 | 5.82 | -0.62 | 6.10 | -0.90 |
| $C_9$-C$\underline{H}_2$ | ∼2.5 | ∼2.8 | -0.3 | ∼3.2 | -0.7 | ∼3.5 | -1.0 |
| $C_{10}$-C$\underline{H}$ | 4.47 | 5.01 | -0.54 | 5.55 | -1.08 | 6.10 | -1.53 |
| $C_{11}$-C$\underline{H}_3$(ax) | 0.96 | 1.62 | -0.66 | 2.23 | -1.27 | 2.94 | -1.98 |
| $C_{11}$-C$\underline{H}_3$(eq) | 1.22 | 2.07 | -0.85 | 2.89 | -1.67 | 3.82 | -2.60 |

$\Delta^{0.25}_{Eu} = \delta_{CCl_4} - \delta^{0.25}_{Eu(fod)_3}$, $\Delta^{0.5}_{Eu} = \delta_{CCl_4} - \delta^{0.5}_{Eu(fod)_3}$, $\Delta^{1.0}_{Eu} = \delta_{CCl_4} - \delta^{1.0}_{Eu(fod)_3}$

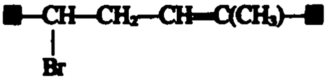


7 8 9

10

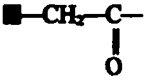
Fig. 3.

two tertiary Me groups at δ 0.87 and 1.20 (each 3 H, s, probably *gem*-dimethyl), one secondary Me group at 1.00 (3 H, d, J = 6.0 Hz), one olefinic Me at 1.55 (3 H, br. s), 2.55 (2 H, m, allylic methylene), 4.53 (1 H, dd, J = 9.7, 8.5, -C$\underline{H}$Br-) and 5.1 (1 H, m, olefinic proton) and ketone group (1703 cm$^{-1}$) in its PMR and IR spectra. Moreover, two-proton singlet at 2.32 revealed the presence of a methylene group adjacent to both a quarternary C and the CO group. Double resonance experiments of the PMR spectrum indicated the presence of the following partial structures E and F in the molecule.



$$\blacksquare\!-\!\underset{\substack{|\\ Br}}{CH}\!-\!CH_2\!-\!CH\!=\!C(CH_3)\!-\!\blacksquare$$

E



$$\blacksquare\!-\!CH_2\!-\!\underset{\substack{\|\\ O}}{C}\!-$$

F

Table 8. Selected chemical shift data for the halogenated chamigrene derivatives

| Compound | $C_{11}-(CH_3)_2$ | $C_7-CH_3$ | $C_{10}-H$ | $C_4-H$ |
|---|---|---|---|---|
| 1 | 0.93, 1.10 | 1.74(br s) | 4.52(dd,J=8.0,8.0 Hz) | |
| 2 | 0.96, 1.22 | 2.00(br s) | 4.47(dd,J=10.0,7.0 Hz) | 4.67(dd,J=9.5,9.5 Hz) |
| 3 | 0.87, 1.20 | 1.55(br s) | 4.53(dd,J=9.7,8.5 Hz) | |
| 4 | 0.95, 1.22 | ca.2.0(br s) | 4.42(dd,J=10.0,7.0 Hz) | 4.78(dd,J=8.5,8.5 Hz) |
| 5 | 0.92, 1.10 | 1.64(br s) | 4.62(dd,J=9.0,7.5 Hz) | |
| 10 | 1.07, 1.16 | 1.19(d,J=7.0 Hz) | 4.15(dd,J=12.0,5.0 Hz) | 4.23(dd,J=11.0,5.0 Hz) |
| 13 | 1.07, 1.16 | 1.21(d,J=7.0 Hz) | 4.21(dd,J=12.0,5.0 Hz) | 4.29(dd,J=13.0,4.0 Hz) |

The structure of 3 has been clarified by the chemical transformation of 1 to 3. Treatment of 1 with boron trifluoride etherate in benzene at room temperature led to the formation of a rearranged product, which was identical with the natural ketone (3) by the mixed m.p. and the comparison of the IR and PMR spectra, and the optical rotation with those of an authentic specimen. From this chemical transformation, the structure of 3 should be represented as 10 - bromo - α - chamigren - 4 - one, in which the stereochemistry of the secondary Me group at C-3 has been shown on the basis of the reaction mechanism as shown in Scheme 2.

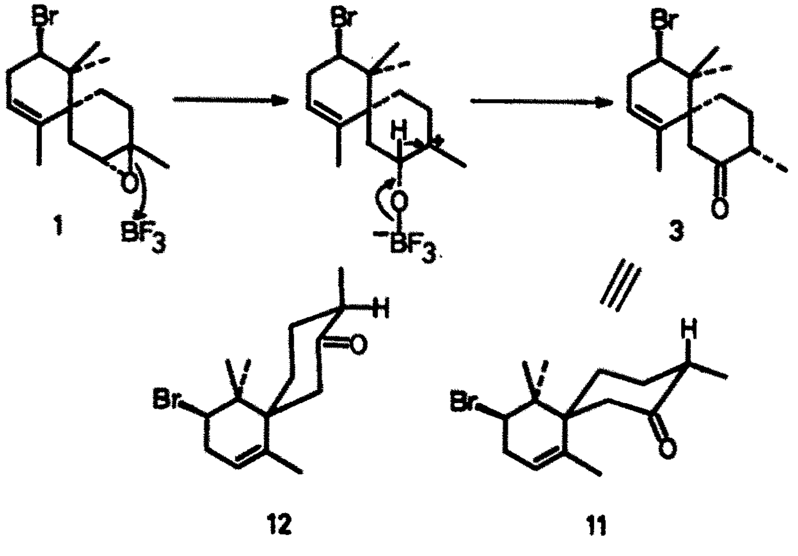
The ORD curve of 3 displayed a negative Cotton effect [a = −93; $[\Phi]_{308}$ = −5200 (trough), $[\Phi]_{268}$ = +4100 (peak)], being expected from the octant projection of formula 11, and offered information on the stereochemistry. Alternative formula 12 for 3, in which the Me group at C-3 certainly possesses an energetically stable equatorial nature, should be discarded since the positive Cotton effect is expected from its octant projection. This observation accepts the formula 11 for 3 and moreover, supports the transformation mechanism from 1 to 3 as shown in Scheme 2 and B-ring in 3 seems to preserve the chair form, being different from 2, because of the disappearance of the interaction between the Me group at C-7 and the axial H at C-4, similar to formula 10.

### *Stereochemistry of* 4,10 - *dibromo* - 3 - *chloro* - *α* - *chamigrene* (4)[7c], 10 - *bromo* - *α* - *chamigrene* (5)[7d,7e] *and* (−)-*α-chamigrene* (6)[13]

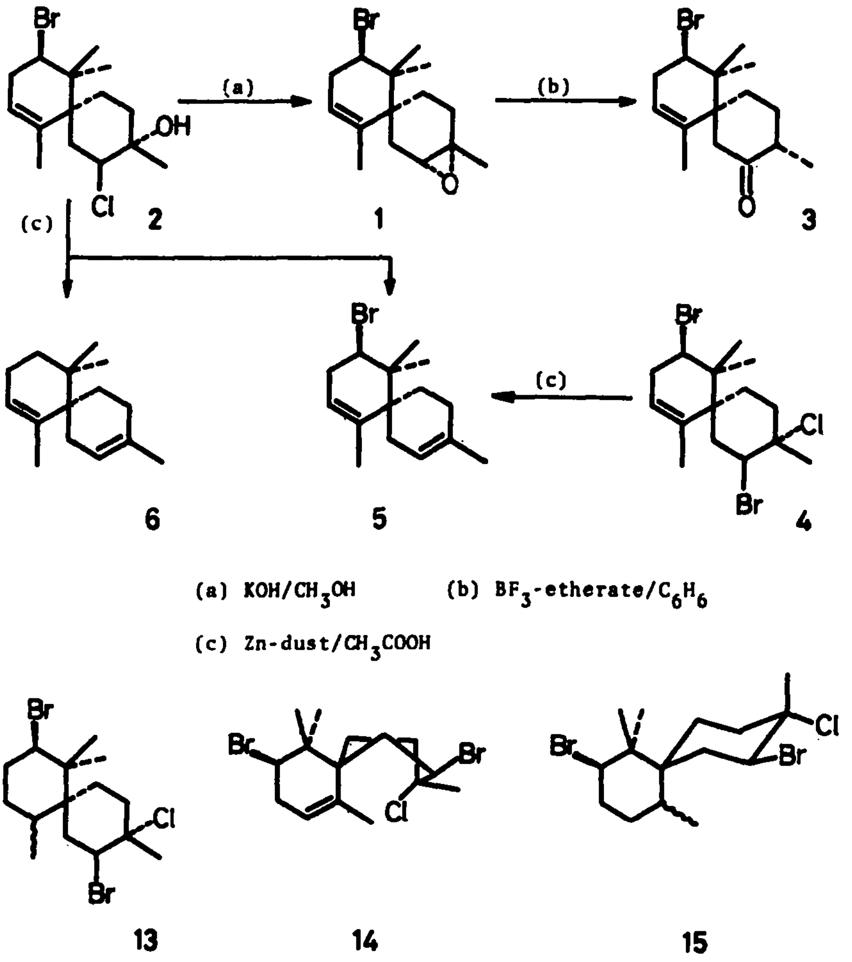
The stereochemistry of the natural products 4 and 5, including the absolute configuration, were determined by the chemical transformation of 2 and 4. Treatment of 2 with Zn-dust in acetic acid afforded 5 and 6. As shown in Scheme 3, the absolute configurations of 5 and 6 should be clear by relating to 2, the absolute configuration of which has been clarified. On the other hand, 4 gave 5 under the same transformation condition and thus the structure of 4, including the absolute configuration, was certified in the same manner as for 5 and 6. Moreover, from the PMR spectral analysis (Table 8) as discussed for 2, the structure of 4 and its hydrogenated product (13) are represented as formula 14 and 15, respectively.

## EXPERIMENTAL

All the m.ps are uncorrected. The UV and IR spectra were measured using a Nihon-Bunko ORD/UV-5 spectrometer and IR-S spectrometer, respectively. The PMR spectra were recorded on a JEOL JNM-PS-100 spectrometer, using TMS as an internal reference in $CCl_4$ and the $^{13}C$ NMR spectra were obtained with a JEOL JNM-FX100 spectrometer in $CDCl_3$. The optical rotations were measured in $CHCl_3$ soln. Aluminum oxide (Merck, activity II–III) and silicic acid (Mallinckrodt) were used for column chromatography.



Scheme 2.



Scheme 3.

*Isolation.* Air dried seaweed (8.5 kg) was extracted with MeOH and the neutral essential oil (90 g) was extensively chromatographed over neutral alumina. The n-hexane fraction was rechromatographed over silicic acid with n-hexane. The earlier fraction consisted of 5,[7d] laurene and isolaurene,[14] and successively eluted fractions contained α-bromocuparene and α-isobromocuparene.[15] Later fractions consisted of 4[7c] and bromoethers.[16] Each fraction was repeatedly chromatographed on a silicic acid column and on preparative silica gel plates to yield 5 (70 mg, 0.0008% dry weight alga) and 4 (150 mg, 0.0018%). The n-hexane-benzene (10:1) fractions were chromatographed on silicic acid. From the earlier benzene eluates, crystalline compounds were obtained and the successively eluted fractions gave pure spirolaurenone[17] (1.2 g, 0.014%) as a colorless oil. The crystals were cautiously recrystallized from MeOH to give 1 (50 mg, 0.0006%) and 3 (50 mg, 0.0006%) and 10 - bromo - β - chamigren - 4 - one[7a] (100 mg, 0.0012%). The ether fractions consisted of an alcoholic mixture and this mixture was acetylated with $Ac_2O$ in pyridine. The acetylated mixture was chromatographed over silicic acid to yield pure 2 (800 mg, 0.009%) along with laurencin[18] and cholesteryl acetate.

10-*Bromo*-3,4-*epoxy*-α-*chamigrene* (1); m.p. 53–54° (from MeOH); $[\alpha]_D -92°$ (*c*, 0.98); UV, $\lambda_{max}^{EtOH}$ only end absorption; IR, $\nu_{max}^{CHCl_3}$ 1660, 1390, 1372, 1183, 1160, 1130, 1110, 1053, 1033, 965 and 830 cm$^{-1}$; mass, *m/e* (relative abundance) 300 and 298 ($M^+$, 3), 219 (19), 218 (40), 200 (38), 185 (41), 175 (19), 159 (38), 157 (44), 135 (54), 133 (74), 119 (100), 105 (74), 91 (65), 77 (43), 69 (51) and 55 (65). (Found: C, 60.09; H, 7.88. $C_{15}H_{23}OBr$ requires: C, 60.23; H, 7.74%).

*Glanduliferol* (2); colorless gum; $[\alpha]_D -21.7°$ (*c*, 1.66); IR, $\nu_{max}^{CHCl_3}$ 3580, 1655, 1400, 1390, 1342, 1130, 1105, 1070, 1045, 990, 980, 928 and 832 cm$^{-1}$; mass, *m/e* 336, 334 ($M^+$, 0.1), 300, 298 (1), 219 (38), 218 (15), 201 (31), 185 (15), 175 (36), 159 (56), 149 (100), 133 (77), 119 (92), 105 (87), 91 (82), 77 (49), 69 (51) and 55 (50).

10-*Bromo*-α-*chamigren*-4-*one* (3); m.p. 78–79° (from MeOH–$H_2O$); $[\alpha]_D -88°$ (*c*, 2.46); UV, $\lambda_{max}^{EtOH}$ 284 nm (ε 30); IR, $\nu_{max}^{Nujol}$ 1695, 1183, 1033, 892, 844, 818 and 795 cm$^{-1}$, $\nu_{max}^{CHCl_3}$ 1703, 1395, 1380, 1183, 890, 840 and 810 cm$^{-1}$; mass, *m/e* 300, 298 ($M^+$, 23), 243, 241 (6), 219 (100), 218 (22), 201 (42), 177 (50), 175 (14), 164 (56), 147 (56), 135 (45), 133 (45), 119 (46), 105 (55), 91 (33), 77 (42), 69 (89) and 55 (54). (Found: C, 60.08; H, 7.83).

4,10-*Dibromo*-3-*chloro*-α-*chamigrene* (4); colorless oil; $[\alpha]_D -14°$ (*c*, 1.45); IR, $\nu_{max}^{film}$ 1389, 1081, 1051, 991, 975, 837, 818 and 790 cm$^{-1}$; PMR, δ 0.95 (3 H, s), 1.22 (3 H, s), 1.66 (3 H, s), *ca* 2.0 (3 H, br. s), 4.42 (1 H, dd, J = 10.0 and 7.0 Hz), 4.78 (1 H, dd, J = 8.5 and 8.5 Hz) and 5.2 (1 H, m); mass, *m/e* 402, 400, 398, 396 ($M^+$, 15), 321, 319, 317 (32), 283, 281 (3), 201 (34), 159 (45), 145 (100), 133 (40), 119 (95), 109 (50) and 91 (89).

10-*Bromo*-α-*chamigrene* (5); colorless oil; $[\alpha]_D -81°$ (*c*, 0.92); IR, $\nu_{max}^{film}$ 1399, 1389, 1379, 1190, 1074, 847, 817 and 790 cm$^{-1}$; PMR, δ 0.92 (3 H, s), 1.10 (3 H, s), 1.64 (6 H, br. s), 4.64 (1 H, dd, J = 9.0 and 7.5 Hz), 5.18 (1 H, m) and 5.38 (1 H, m); mass, *m/e* 284, 282 ($M^+$, 7), 216, 214 (48), 203 (11), 202 (7), 135 (100), 119 (42), 109 (24) and 91 (25).

*Treatment of* 1 *with* 1 M *ethanolic* KOH. A soln of 1 (16 mg) in 1 M ethanolic KOH (2 ml) was refluxed for 30 min in a stream of $N_2$. After being cooled, the mixture was extracted with ether. The ethereal soln was washed with water and dried over $Na_2SO_4$. After evaporation of the solvent, the residual oily material was chromatographed on silicic acid to give a conjugated cyclohexadiene (5 mg) as a colorless oil; $[\alpha]_D +110°$ (*c*, 0.95); UV, $\lambda_{max}^{EtOH}$ 264 nm (ε 2900); IR, $\nu_{max}^{CHCl_3}$ 1603, 1385, 1362, 1100, 1051, 1031, 1007, 990, 965, 918, 888 and 840 cm$^{-1}$; PMR, $\delta$ 0.96 (3 H, s), 1.09 (3 H, s), 1.22 (3 H, s), 1.70 (3 H, br. s), 2.79 (1 H, d, J = 4.0 Hz), 5.0–5.7 (3 H, m); mass, *m/e* 218 (M$^+$, 29), 203 (17), 200 (10), 185 (16), 175 (25), 159 (44), 157 (36), 133 (73), 119 (100), 105 (91), 91 (77), 77 (52), 69 (35) and 55 (63).

*Treatment of* 1 *with boron trifluoride etherate.* A soln of 1 (32 mg) in benzene (0.5 ml) was treated with $BF_3$–$Et_2O$ (0.2 ml) at room temp. After 5 min, water was added and the mixture was extracted with ether. The ethereal soln was washed with water and dried over $Na_2SO_4$. After evaporation of the solvent, the residue was chromatographed over silicic acid to yield crystals of 3 (20 mg); m.p. 76–77° (from MeOH); $[\alpha]_D -90°$ (c, 0.59); the IR and PMR spectra were superimposable upon those of natural compound 3.

*Treatment of* 2 *with 5% methanolic* KOH. A soln of 2 (55 mg) in 5% methanolic KOH (3 ml) was allowed to stand at room temp. for 7 min. After being treated in the usual manner, the products were chromatographed on silicic acid to give crystals of 1 (22 mg); m.p. 52–53° (from MeOH); $[\alpha]_D -79°$ (*c*, 0.96)); the IR and PMR spectra were superimposable upon those of natural 1.

*Hydrogenation of* 2. The hydrogenation of 2 (30 mg) was performed in EtOH over $PtO_2$-catalyst. After removal of the catalyst and the solvent, the residual oil was chromatographed on silicic acid to give 10 (16 mg) as a colorless oil; $[\alpha]_D +16°$ (*c*, 0.78); IR, $\nu_{max}^{CHCl_3}$ 3600, 1390, 1343, 1315, 1100, 1080, 1017, 990, 987, 930, 890, 866, 854 and 835 cm$^{-1}$; PMR, $\delta$ 1.07 (3 H, s), 1.16 (3 H, s), 1.19 (3 H, d, J = 7.0 Hz), 1.29 (3 H, s), 4.15 (1 H, dd, J = 12.0 and 5.0 Hz) and 4.23 (1 H, dd, J = 11.0 and 5.0 Hz); mass, *m/e* 338 and 336 (M$^+$).

*Treatment of* 2 *with zinc-dust-acetic acid.* To a soln of 2 (61 mg) in AcOH (5 ml) was added Zn-dust (150 mg), and the mixture was stirred for 3 hr at 60° (bath temp). After cooling and filtrating off Zn-dust, the mixture was extracted with ether. The ethereal soln was washed with water, 5%-$NaHCO_3$aq and finally with water, dried over $Na_2SO_4$, and evaporated. The residual oil was chromatographed on silica gel plates with n-hexane to give 6 (8 mg) and 5 (4 mg) (28 mg of 2 was recovered): 6, colorless oil, $C_{15}H_{24}$ (*m/e* 204; M$^+$), $[\alpha]_D -30°$ (*c*, 0.36); the IR and PMR spectra were identical with those of $\alpha$-chamigrene: 5, colorless oil, $[\alpha]_D -92°$ (*c*, 0.39); the IR and PMR spectra were superimposable upon those of natural 10 - bromo - $\alpha$ - chamigrene (5).

*Treatment of* 4 *with zinc-dust-acetic acid.* To a soln of 4 (29 mg) in AcOH (2 ml) was added Zn-dust (100 mg), and the mixture was stirred for 2.5 hr at 50° (bath temp). After cooling and filtrating off Zn-dust, the mixture was extracted with ether. The ethereal soln was washed with water, 5%-$NaHCO_3$aq and finally with water, dried over $Na_2SO_4$, and evaporated. The residual oil was chromatographed on silica gel plates with n-hexane to yield 5 (7 mg) (10 mg of 4 was recovered), colorless oil, $[\alpha]_D -110°$ (*c*, 0.48); the IR and PMR spectra were superimposable upon those of natural 5.

*Hydrogenation of* 4. The hydrogenation of 4 (35 mg) was performed in EtOH over $PtO_2$-catalyst. After removal of the catalyst and the solvent, the residual oil was chromatographed over silicic acid to yield 13 (19 mg); $[\alpha]_D +42°$ (*c*, 1.4); IR, $\nu_{max}^{CHCl_3}$ 1400, 1390, 1100, 990, 969, 867 and 852 cm$^{-1}$; PMR, $\delta$ 1.07 (3 H, s), 1.16 (3 H, s), 1.21 (3 H, d, J = 7.0 Hz), 1.68 (3 H, s), 4.21 (1 H, dd, J = 12.0 and 5.0 Hz) and 4.29 (1 H, dd, J = 13.0 and 4.0 Hz); mass; *m/e* 402, 400 and 398 (M$^+$).

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