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Cartilagineol, the Fourth Lineage of *Laurencia*-derived Polyhalogenated Chamigrene

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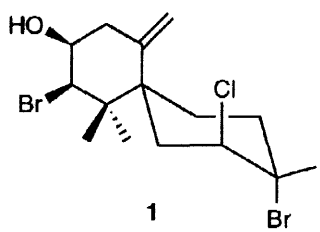
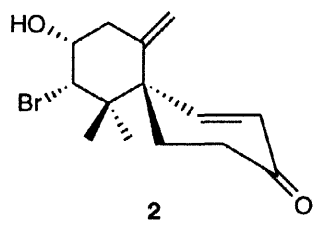
Abstract: A revised regiochemistry and the absolute configuration are established for cartilagineol (formerly *allo*-isoobtusol). This revised structure renders cartilagineol the first example of the fourth stereochemical type of *Laurencia*-derived polyhalogenated chamigrene in support of current biogenetic theory. Earlier misassigned NMR data for ma'ilione is corrected.

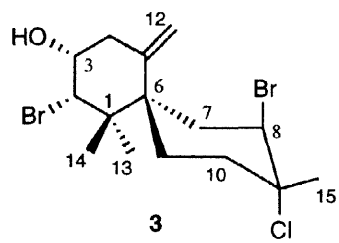
A recent paper by Juagdan *et al.*[1] described two new chamigrene metabolites, *allo*-isoobtusol (**1**) and ma'ilione (**2**), isolated as minor components of a Hawaiian collection of *Laurencia cartilaginea*. Guella *et al.*[2] have questioned the structural assignment for *allo*-isoobtusol suggesting structure **3** as a better fit to the physical data as well as to biogenetic theory. We have isolated both of these compounds, along with known vinyl bromides **4** and **5**,[3-5] from *Laurencia* sp. collected at Taytay, Philippines. We wish to report that **3** is the correct structure for *allo*-isoobtusol, rechristened cartilagineol.[2]



1



2



3

Cartilagineol (15 mg), colorless crystals, mp 62-63°, $[\alpha]_D$ -32° (c 0.253, $CHCl_3$), was separated from **4** by PTLC on silica (hexane:isopropanol, 45:1). Its molecular formula was established as $C_{15}H_{23}Br_2ClO$ by HREIMS. The ^1H and ^{13}C NMR spectral data (Table 1) were identical to those reported,[1] but the assignments for the halogenated carbons C-8 and C-9 have been reversed. Based on carbon chemical shift values and the HMQC spectrum, the quaternary halide at C-9 can be assigned as chlorine (δ_C 73.3) and the methine halide at C-8 as bromine (δ_C 57.1). Although bromine and chlorine display similar α-shift effects at C-1 in 1-methyl-1,2-dihalocyclohexanes, the α-shift effects at C-2 are significantly different; the bromomethine carbon generally appears at least 5 ppm upfield of its chloro analog.[6]

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To provide further evidence for both the regio- and stereochemistry of cartilagineol, an x-ray crystal structure was carried out. Crystals of **1** were grown by slow evaporation of a hexane solution at 5°C. A crystal 0.4 x 0.2 x 0.15 mm was selected and mounted on a glass fiber for data collection.[7] The crystal decomposed fairly quickly in the x-ray beam (38% decrease in standard reflection intensity after 25 hrs) and the data collection was terminated early. The compound crystallized in the monoclinic space group $P2_1$ (a=15.963Å, b=7.118Å, c=16.427Å, β=90.58°) with two independent molecules in the asymmetric unit (Z=4). Only the Br, Cl and O atoms were refined anisotropically. The final least squares refinement gave R=0.126 for 1534 F>4σ (0.152 for all 2097 data) and 194 parameters. While the data set was insufficient for complete refinement, the relative stereochemistry of the molecule is clear and shown in Fig. 1. The hydrogens at the stereogenic centers (in calculated positions) have been included for clarity. Both molecules in the asymmetric unit show the same stereochemistry.

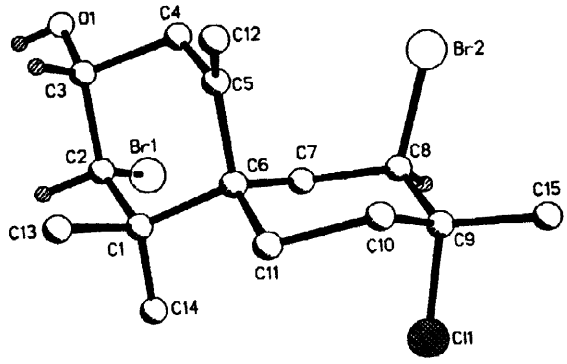
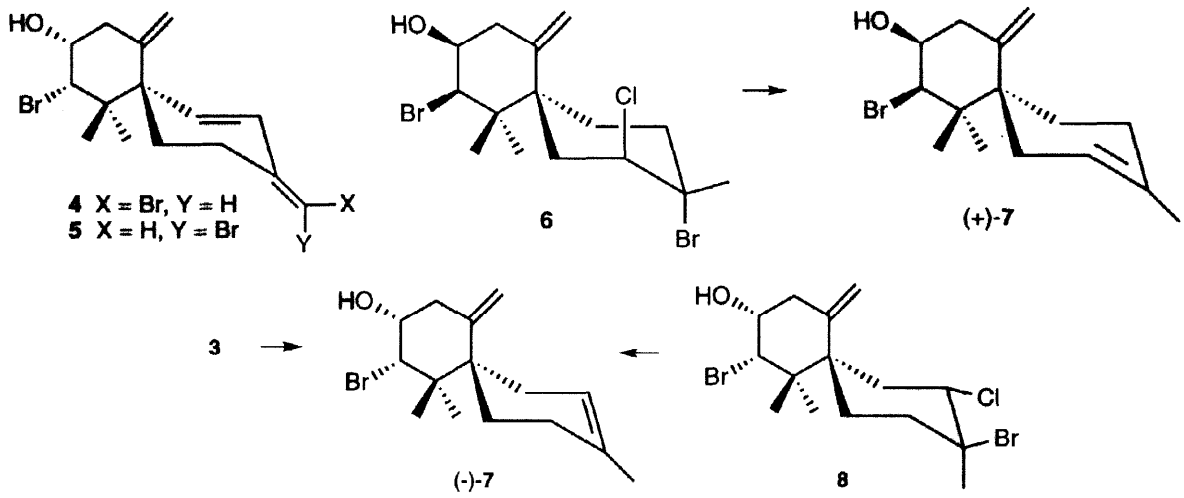


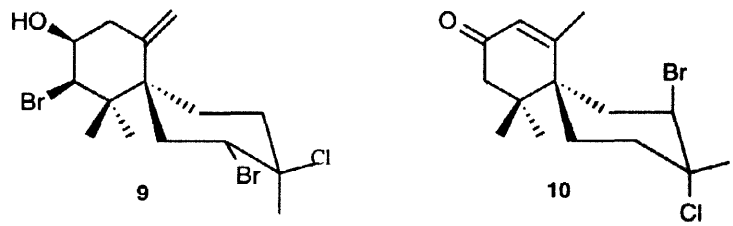
Figure I: Molecular Structure of 3

Although the x-ray data collection did not allow the determination of the absolute configuration of cartilagineol, several other lines of evidence strongly support the configuration shown in **3** (2*S*, 3*R*, 6*S*, 8*R*, 9*R*). First, as pointed out by Guella *et al.*,[2] the optical rotation of cartilagineol is essentially the same as that of isoobtusol (**6**) (+33°) but opposite in sign.[8] As the interchange of halogens at C-8 and C-9 does not affect the rotation,[2,9] this indicates that **3** and **6** have an enantiomeric relationship. Second, the optical rotation of **5** isolated from the present extract was -38° in agreement with the literature value of -33°.[4,10] The absolute configuration of **5** follows from its spontaneous equilibration with **4**, whose absolute configuration has been established by x-ray.[3b] Third, when we treated cartilagineol (**3**) with Zn/AcOH, (-)-**7** (deschloroelatol) was produced. Both enantiomers of **7** are known[8,11] and their absolute configurations are established by their method of preparation: the (-)-isomer from $LiAlH_4$ reduction of obtusol (**8**) and the (+)-isomer from Zn/AcOH reduction of isoobtusol (**6**).[8]

That cartilagineol is correctly represented by structure **3** is of biogenetic significance. Current theory predicts the existence of four stereochemical types for the polyhalogenated *Laurencia*-derived chamigrenes;[2,12] to date, three types have been reported. Examples of these three types are obtusol (**8**), isoobtusol (**6**), and rogiolol (**9**), all found in distinct *Laurencia* collections. Cartilagineol represents the missing fourth stereochemical type. Its discovery lends credence to the biogenetic theory and to the possibility that *Laurencia's* secondary metabolites may be useful in sorting out the confused taxonomy of this genus.[2]



In addition to cartilagineol, ma'ilione (**2**) (20 mg) and vinyl bromides **4** (4 mg) and **5** (11 mg) were isolated from the extract. Ma'ilione, colorless crystals, mp 135-136°, $[\alpha]_D$ -20° (c 0.196, $CHCl_3$), was obtained by PTLC on silica (hexane:isopropanol, 15:1). Its NMR spectral data were identical to those reported.[1] However, the original data contained several misassignments which are corrected in Table 1. In particular, the enone vinyl hydrogens were reversed as were the C-13 methyl and the C-11 methylene carbons. The HMQC spectrum clearly distinguishes these latter two carbons. Our optical rotation value was also significantly different from that reported (-20° *vs.* -100°) and may possibly be explained by the larger size of our sample (9.8 mg *vs.* 0.4 mg) and its greater purity (crystals *vs.* oil).



Enone **10**, $[\alpha]_D$ +9.4° (c 0.05, $CHCl_3$), appears as an artifact produced during the purification of cartilagineol. HRFABMS established its formula as $C_{15}H_{22}BrClO$. Its structure was deduced from an analysis of the ^1H, ^{13}C and COSY spectra.[13] In the ^1H NMR spectrum of **10**, the C-2 and C-3 methine signals and the terminal vinyl hydrogen signals of cartilagineol were replaced by a deshielded vinyl hydrogen (δ 5.84) and a vinyl methyl (δ 2.19). HBr loss followed by isomerization would convert **3** to **10**, and all of the spectral data support this conclusion. Such a process has ample precedence in these systems.[3a,9,14,15]

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Table 1: ^{13}C and ^{1}H NMR Data for Cartilagineol 3 and Ma'ilione 2 in $CDCl_3$

	3		2	
Pos.	$^{13}C^a$	$^{1}H^b$	$^{13}C^a$	$^{1}H^b$
1	43.7 (s)	--	42.7 (s)	–
2	76.4 (d)	4.38 (dd, 1.7, 3.7)	68.8 (d)	4.58 (d, 3.0)
3	69.6 (d)	3.65 (br dddd, 3.7, 4.1, 11.3, 12.1)	71.7 (d)	4.18 (m)
4	39.4 (t)	2.42 (br dd, 4.0, 12.1)	38.4 (t)	2.68 (dd, 3.5, 13.0)
		2.70 (t, 12.1, 12.1)		2.71 (br d, 13.0)
5	142.2 (s)	–	141.7 (s)	–
6	44.0 (s)	–	51.8 (s)	–
7	33.7 (t)	2.79 (dd, 4.1, 16.0)	152.9 (d)	7.00 (dd, 1.4, 10.8)
		3.06 (br d, 15.9)		
8	57.1 (d)	4.44 (br s)	131.1 (d)	6.10 (d, 10.6)
9	73.3 (s)	–	198.7 (s)	–
10	32.4 (t)	1.77 (ddd, 4.5, 5.5, 12.7)	34.2 (t)	2.34 (2H, m)
		2.32 (ddd, 4.8, 12.7, 13.0)		
11	24.3 (t)	1.70 (ddd, 4.5, 6.1, 13.7)	26.3 (t)	2.15 (m)
		2.02 (dt, 4.8, 13.5, 13.5)		2.20 (m)
12	114.7 (t)	4.95 (s)	117.9 (t)	4.84 (s)
		5.19 (s)		5.17 (br s)
13	23.3 (q)	1.03 (s)	26.9 (q)	1.04 (s)
14	24.4 (q)	1.29 (s)	21.4 (q)	1.29 (s)
15	33.1 (q)	1.74 (s)	--	–
OH	--	2.23 (d, 11.2)	--	2.26 (br s)

[a] Recorded at 50 MHz, $CDCl_3$ as internal standard (δ 77.0). Multiplicity was based on the JMODXH spectra.
[b] Recorded at 500 MHz.

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13. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.02 (s), 1.15 (s), 1.79 (s), 2.07 (dd, 4.5, 15.4 Hz), 2.12 (br d, 18.3 Hz), 2.19 (d, 1.2), 2.22 (m), 2.28 (m), 2.33 (m), 2.38 (m), 2.47 (br d, 18.2), 2.92 (dd, 4.7, 15.6), 4.62 (dd, 4.5, 7.6), 5.84 (br s); ^{13}C NMR ($CDCl_3$, 50 MHz, carbonyl carbon not observed) δ 23.9 (t), 24.1 (q), 26.1 (q), 28.5 (q), 28.8 (q), 37.0 (t), 39.4 (t), 41.9 (s), 44.6 (s) 49.2 (t), 58.5 (d), 71.3 (s), 127.9 (d), 168.6 (s).
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