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EVIDENCE FOR THE BIOGENESIS OF HALOGENATED CHAMIGRENES FROM THE RED ALGA LAURENCIA OBTUSA[1]

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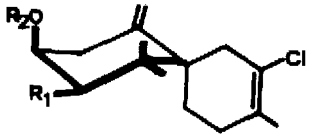
From ether extracts of fresh Laurencia obtusa (Huds) Lamoroux, we isolated the five new halogenated sesquiterpenes II-VI together with the already known elatol (I)[2] and caespitol (VII)[3]. The structures and absolute configurations II-VI were determined by chemical correlation with elatol (I) which has been studied by X-ray methods[2,3].

Compound II, $[\alpha]_D$+98, was analyzed as $C_{15}H_{23}OCl$, m/e M^+ 256, 254; IR 3400, 3100, 1650, 900 and 820 cm^{-1}; PMR δ 0.92, 1.05, 1.74 (s, 3H each), 4.06 (m, 1H, $W_{1/2}$ 7Hz), 4.81 and 5.11 (bs, 1H each). Compound II was prepared by reduction of elatol (I), $[\alpha]_D$+91, with Bu_3SnH in o-xylene and a catalytic amount of AIBN at 90°. Reduction of II with Na/tert BuOH/THF gave the alcohol X which, on purification, gave its acetate XI, mp 55°, $[\alpha]_D$+85.

Compound III was isolated by n-hexane recrystallization of the partly crystalline ether extract residue, mp 118-120°, $[\alpha]_D$+33, and analyzed as $C_{15}H_{23}OBr_2Cl$, m/e M^+ 416, 414, 412; IR (KBr) 3300, 3100, 1640 and 880 cm^{-1}; PMR δ 1.06, 1.35, 1.92 (s, 3H each), 3.65 (1H, m, $W_{1/2}$14Hz), 4.42 (2H, m, $W_{1/2}$5Hz), 4.92 and 5.19 (s, 1H each). The closely spaced multiplets for the protons at C2 and C10 (δ 4.42) were consistent with axial Cl and Br atoms and, hence, equatorial hydrogens. Comparison of the chemical shifts of the methyl group at C2 in III (δ 1.92) with those noted in isocaespitol (VIII)[4], in which the halogens exist in the diaxial conformation, indicates that the second Br atom is located in the tert position. When compound III in hexane was stirred for 78 hrs at r.t. over silica gel, a *syn* dehydrobromination was produced and elatol (I), $[\alpha]_D$+90, formed quantitatively. Reduction of III with Zn/AcOH in ether at 0° yielded a mixture of the partially dehalogenated compound IX, mp 94-95°, $[\alpha]_D$+82, and the triene XII, $[\alpha]_D$+33.

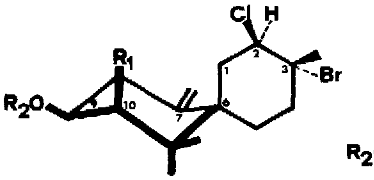
Compound IV (acetate), mp 102-104°, $[\alpha]_D$+73, was analyzed as $C_{17}H_{26}O_2BrCl$, m/e M^+ 380, 378, 376; IR (KBr) 3080, 1740, 1640, 880 and 700 cm^{-1}; PMR δ 0.88, 1.02, 1.92, 2.00 (s, 3H each), 4.45 (1H, bs, $W_{1/2}$5Hz), 4.80 (1H, m, $W_{1/2}$14Hz), 4.86 and 5.12 (s, 1H each). Compound IV (R_2'=Ac) was quantitatively transformed into II (R_2'=Ac), $[\alpha]_D$+96, by treatment with silica gel at r.t. Reduction of IV (R_2'=Ac) with Zn/AcOH in ether at 0° gave XI, $[\alpha]_D$+85, identical to a sample from I.

Compound V, mp 145-146°, $[\alpha]_D$+10, was analyzed as $C_{15}H_{23}OBr_2Cl$, m/e M^+ 416, 414, 412; IR (KBr) 3600, 3100, 1640, 860 cm^{-1}; PMR δ 1.08 (s, 6H), 1.82 (s, 3H), 4.12 (1H, m, $W_{1/2}$6Hz), 4.50 (1H, d, J=3Hz), 4.70 (1H, dd, J=12 and 5Hz). Reduction of V with LAH in ether at r.t. yielded the partially dehalogenated compound XIV, $[\alpha]_D$-82, and the tridehalo-alcohol XV, which was acetylated to give a crystalline acetate XVI, mp 56-57°, $[\alpha]_D$-85. Treatment of V with Zn/AcOH for 48 hrs at r.t.



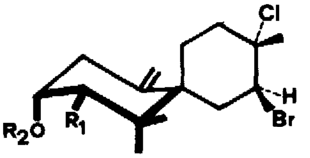
I; R_1 = Br, R_2 = H

II; R_1 = H, R_2 = H



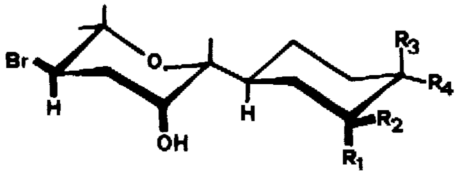
III; R_1 = Br, R_2 = H

IV; R_1 = H, R_2 = H



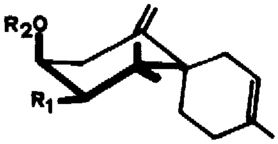
V; R_1 = Br, R_2 = H

VI; R_1 = H, R_2 = H



VII; R_1 = H, R_2 = Br, R_3 = CH_3, R_4 = Cl

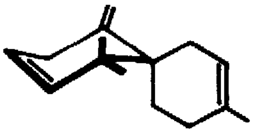
VIII; R_1 = Cl, R_2 = H, R_3 = Br, R_4 = CH_3



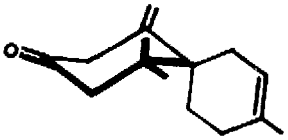
IX; R_1 = Br, R_2 = H

X; R_1 = H, R_2 = H

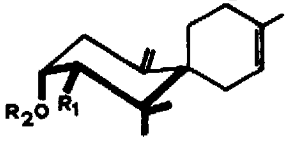
XI; R_1 = H, R_2 = Ac



XII



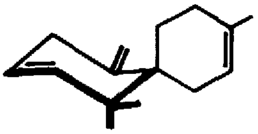
XIII



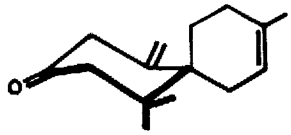
XIV; R_1 = Br, R_2 = H

XV; R_1 = H, R_2 = H

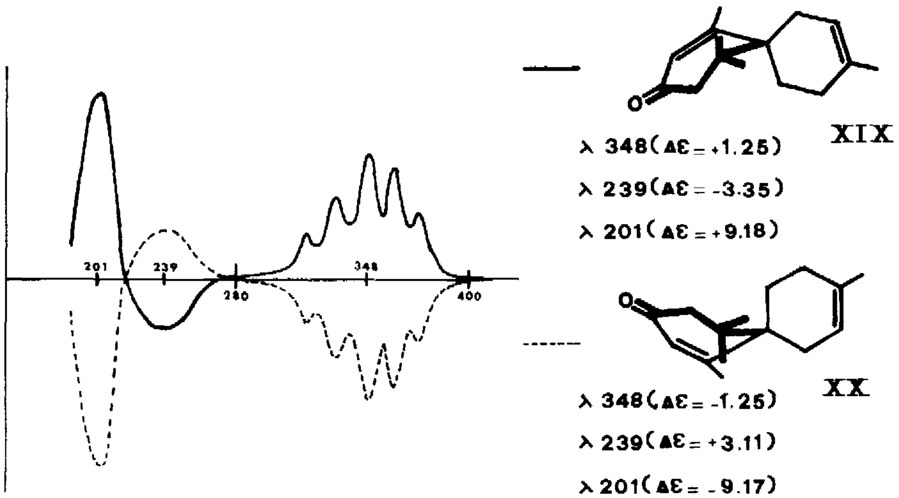
XVI; R_1 = H, R_2 = Ac



XVII



XVIII

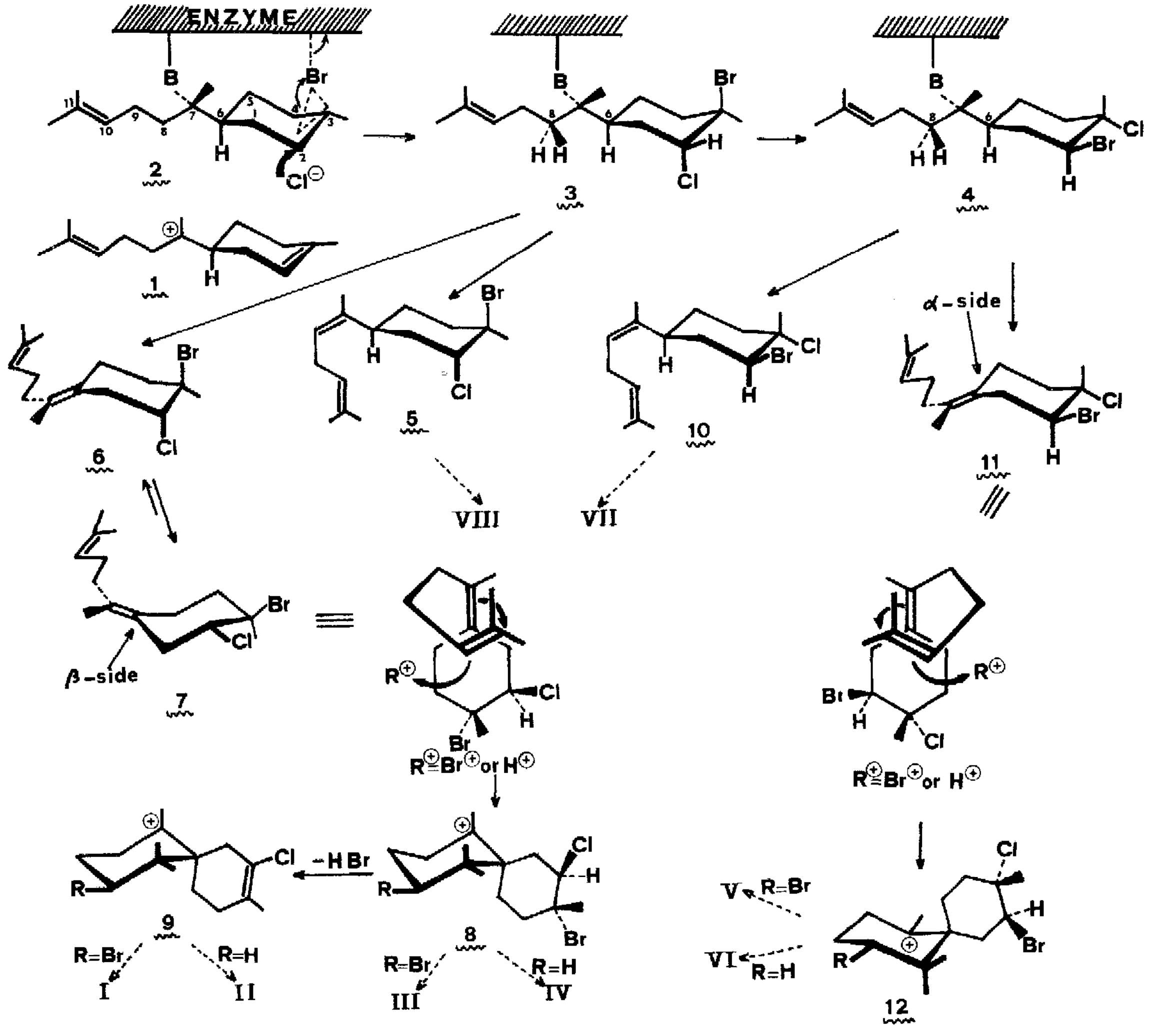


λ 348 (Δε = +1.25)
λ 239 (Δε = -3.35)
λ 201 (Δε = +9.18)

λ 348 (Δε = -1.25)
λ 239 (Δε = +3.11)
λ 201 (Δε = -9.17)

FIGURE 1

gave a single hydrocarbon XVII, $[\alpha]_D$-32.
Compound VI (acetate), mp 81-82°, $[\alpha]_D$+11, was analyzed as $C_{17}H_{26}O_2BrCl$, m/e M^+ 380, 378, 376; IR δ (KBr) 3090, 1740, 1650, 880 and 750 cm^{-1}; PMR δ 0.90, 0.98, 1.84, 2.03 (s, 3H each), 4.34 (1H, dd, J=12 and 5Hz), 4.85 (1H, m, $W_{1/2}$6Hz), 4.90 and 5.32 (bs, 1H each). Reduction of VI with LAH in ether at r.t. after acetylation gave the compound XVI, $[\alpha]_D$-86, identical with a sample from V. The reduction products of V (XIV, XV, XVI and XVII) have spectroscopic (MS, PMR, IR) characteristics identical to those of the corresponding derivatives of III and IV (IX, X, XI and XII), the only difference being that the optical rotations are diametrically opposed. The opposite stereochemistry which differentiates these series of compounds is immediately apparent on comparison of the CD curves of the α,β-unsaturated ketones XIX and XX (fig 1) which are optical antipodes[5]. Chromic acid oxidation of III gave an unstable ketone which was further reduced with Zn/AcOH to the tridehaloketone XIII, isomerized by refluxing with oxalic acid in MeOH to the α,β-unsaturated ketone XIX, $[\alpha]_D$+80.
Oxidation of compound XV with CrO_3/H^+ gave XVIII which was isomerized to XX, $[\alpha]_D$-80, by the same process.
The biogenetic sequence for these sesquiterpenes is hypothesized in Scheme 1. The fact that caespitol (VII) and products with a chamigrene skeleton can be found together suggests a bisabolonium ion precursor, at least in *L. obtusa*[6]. The formation of (+)-β-chamigrene and (-)-β-chamigrene derivatives can be rationalized as follows: the bisabolonium ion (1) trapped by a basic site of the cyclase (as in 2) is enzymatically brominated at C(2) with concerted antiparallel addition of $Cl^{(-)}$ to give the *trans*-diaxial bromochloride system indicated in (3). At this stage, part of the *trans*-diaxial bromochloride rearranges by a dyotropic process[7] to the more stable *trans*-diequatorial system indicated in (4). Deprotonation at C(8) in (3) (or 4) gives the α-bisabolene 5 (or 10), precursor of isocaespitol (VIII) [or caespitol (VII)][4]. Deprotonation at C(6) produces the γ-bisabolene intermediates 6 and 11. Steric and conformational factors operate at this level to make the next stage of Br^+ (or H^+)-induced carbocyclization take place on the β face of 6⇄7 and the α face of 11, giving rise to the carbonium ions 8, 9 and 12, from which the sesquiterpenes I-VI, described here, are derived.
This biogenetic theory postulates a (-) absolute configuration for the β-chamigrene skeleton whenever the bromochloride system is *trans*-diequatorial, and all the halogenated chamigrene derivatives with known absolute configurations isolated from *Laurencia*, such as pacifenol[8a], prepacifenol[8b], prepacifenol epoxide[9], acetoxy-intricatol[10] plus those reported here, conform to this rule. Similarly when there is a *trans*-diaxial bromochloride (or vinyl chloride) system, the absolute configuration of the β-chamigrene skeleton should be (+), which is borne out by elatol[2] and the products II, III and IV, as described above.



SCHEME 1: possible sequence in the biosynthesis of sesquiterpenes from the marine alga *Laurencia obtusa*

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