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LAURENCIA SESQUITERPENE BIOGENETIC-TYPE INTERCONVERSIONS[1]

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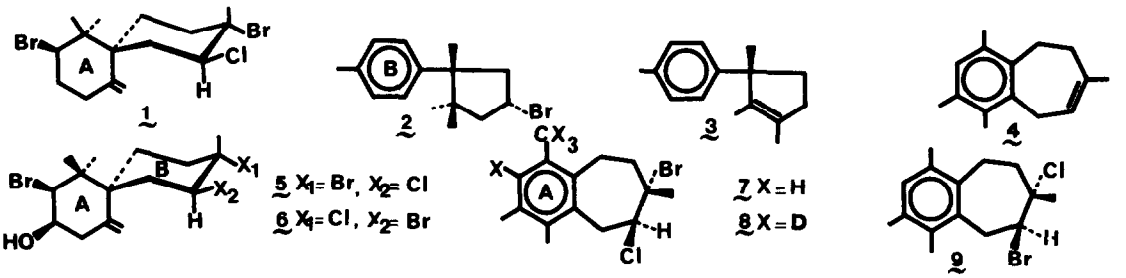
SUMMARY Several aromatic sesquiterpenes from Laurencia algae were prepared from chamigrene skeleton precursors. Chemical evidence was adduced to support a biogenetic-type scheme for the synthesis of perforenol and perforene. By means of x ray analysis the structure and absolute configuration of one of the intermediates was established.

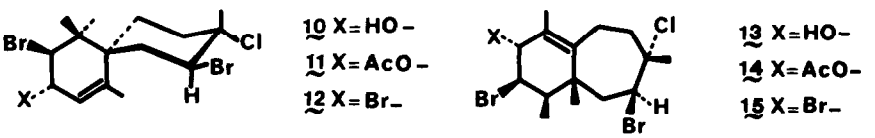
Since it is still impossible to carry out real biosynthetic studies of the macro algae[2], the biogenetic routes accounting for the many sesquiterpene skeletons isolated from different Laurencia algae extracts are at the best only speculations. Nonetheless, it has been repeatedly postulated that these skeletons are derived from a common chamigrene precursor, by simple or complex, but invariably plausible rearrangements[3]. The most accurate way of checking these hypothesized biogenetic routes until true biosynthetic studies become feasible is by the chemical transformation of any proposed intermediate which can be found in the extracts. 100% yield and stereospecificity in such rearrangements indicate the likelihood of the biological process taking place in a similar way.

Parallels between the chemical and biological processes are expected in the formation of the aromatic sesquiterpenes isolated from these algae since it is reasonable to assume that the aromatization is the impelling force which induces and controls the rearrangement and hence, the chemical and biological formation of these skeletons. This paper deals with the biogenetic-type transformations of chamigrene skeleton compounds to cuparane skeletons: (+)-isobromocuparane (2)[4], rearranged cuparane, (+)-isolaurene (3)[5] and perforene (4)[6].

The treatment of obtusane (1)[7] with TsOH/Be under reflux led to the formation of abundant (+)-isobromocuparane (2), $\{\alpha\}_D$+98°, which, by subsequent treatment with silica gel, was transformed into (+)-isolaurene (3), $\{\alpha\}_D$+108°. Obtusol (5)[8], when refluxed with TsOH/Be, gave the compound 7[9] which by a later reaction with Zn/AcOH formed 4, identical to the product obtained under the same conditions from perforene (9)[6]. This result shows that the natural product 9 may also be obtained biogenetically from a chamigrene precursor such as 6 via a similar rearrangement. When obtusol (5) was rearranged using D_2SO_4/nitromethane, the deuterium incorporations seen in 8 were observed[10].



These transformations took place with 100% yield and stereospecificity and under the specified reaction conditions no separable intermediates were identified. The oxygenated function at C-3 is most important as its presence or absence determines whether the product isolated will be the result of the aromatization of Ring A or Ring B of the original chamigrene. The transformation reactions of 1 to 2 and 3 were quite clear and needed no further attention; but those to 9 were less simple and were studied more closely. In order to analyze the transformations which give rise to the perforene skeleton step by step, rearrangements were carried out on the hypothesized and other natural intermediate reagents, in this case 10[11] and 13[12] in very mild acid conditions.



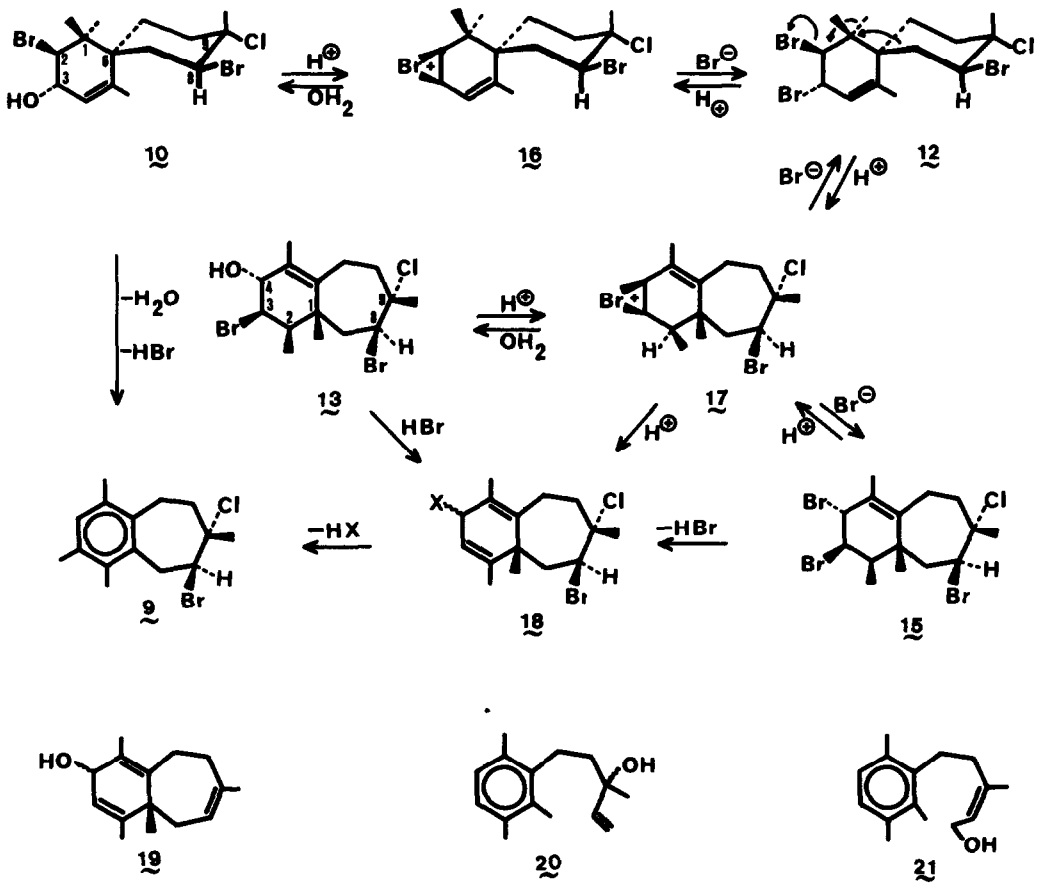
The treatment of the compound 10 (or 13) with AcOH/$LiClO_4$ at ∿40° produced a copious transformation to perforene (9). The same reaction applied to 10 at 0° gave a mixture of 11, 12, 14, 15 and 9, and these, when isolated were transformed largely to 9 by performing the reaction at 40°. 13, treated with AcOH/$LiClO_4$ at 0° gave a mixture of 14, 15 and 9 which was homogenized to 9 when the temperature was raised to 30°. Treatment of 12 (or 15) with AcOH in ether produced compound 11 (or 14) and the same substances treated with silica gel formed alcohol 10 (or 13) in 100% yield. The acetates 11 and 14 were identical with those formed from 10 and 13, respectively, by treatment with Ac_2O/Py. 12 and 15 were identical with the products obtained from 10 and 13, respectively, by PBr_3 in ether treatment. To check the stereoselectivity of the reactions shown independently, the tribromoderivative 15 was subjected to x ray diffraction studies.

The conclusions drawn from our results are shown in Scheme I where a possible biogenetic scheme is outlined which would account for the formation of perforenol (13) and perforene (9) from the common chamigrene precursor 10. In view of the chemical reactivity observed in 10 and 13 it is possible that the bromine atom at C-3 and the OH group at C-4 in 13 may be due to intermolecular substitutions. The regio- and stereoselectivity seen in these substitutions show that the ions 16 and 17 are true reaction intermediates.

In the final stages of the transformation detailed in I (18 to 9) it is clear that prior chlorobromination of the chamigrene precursor is necessary for the aromatization to take place by 1,2 emigration of the methyl followed by deprotonation. The trienol 19[13] upon treatment with silica gel gave a 1:1 mixture of the compounds 20 and 21[14], compound 20 proving identical with the natural

metabolite Compound-B isolated by Erickson *et al*[15] from *L nidifica*.

SCHEME 1



Compound 15, $C_{15}H_{22}Br_3Cl$, crystallized in the space group $P2_1$ with two molecules in a cell, dimensions: a=9·583(1), b=14·668(2), c=6·2896(3) Å, β=101·9(3)°. The intensity of 2619 Bijvoet pairs with θ<25° was measured on an automatic single-crystal diffractometer using graphite monochromated MoKα radiation (0·7107 Å). No crystal decomposition was observed during the experiment. Data were corrected for Lorentz and polarization effects but not for absorption. 2121 Bijvoet pairs with I>2σ(I) were considered observed and used to refine the crystal structure which was solved by the heavy-atom method. The hydrogen atoms, found on a difference map, were included in the last weighted anisotropic least-squares refinement (isotropic for H atoms). The final unweighted and weighted disagreement indices for the right absolute configuration were R=·064 and R_w=·070, respectively. The absolute configuration was calculated by comparing the 118 more relevant Bijvoet pairs which gave an averaged Bijvoet difference of 1·52 (4·43 for the enantiomorph) and an averaged Bijvoet ratio of ·11 (·33). This molecule coincides with that of perforenol (13) where the substituent at C-4 is OH instead of Br (Figure 1). Both molecules have the same absolute configuration and show no significant differences in bond lengths, bond angles and torsions [12]. Only

near C-4 are there slight but significant variations due to the different substituents.

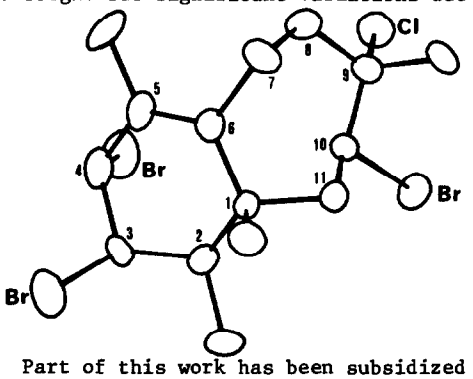


FIGURE 1

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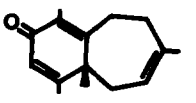
9 Compound 7: oil, $\{\alpha\}_D$+9°, $C_{15}H_{20}BrCl$, M^+ at m/e 314, 316, 318; IR ($CHCl_3$) cm^{-1} 2935, 1450, 1380 and 935; PMR (δ $CDCl_3$) 1·92, 2·20 (s, 3H each), 2·26 (s, 6H), 4·60 (d, 1H, J=7Hz), 6·85 (s, 1H).

10 The deuterium incorporation was measured by MS and PMR.

11 W Fenical *Phytochemistry* 15 511 (1976) Compound 10 has been isolated in this laboratory as a minor constituent from the alga *L perforata*.

12 A G González J M Aguiar J Darias E González J D Martín V S Martín C Pérez J Fayos and M Martínez-Ripoll *Tetrahedron Letters* 3931 (1978)

13 Compound 19 was obtained in abundance by the LAH reduction of a dienone which had been formed by treating perforenone with 1 equiv. DDQ and 2 equiv. benzoic acid in benzene under reflux. {A G González J Darias and J D Martín *Tetrahedron Letters* 3375 (1977)}



14 Alcohol 21: oil, $C_{15}H_{20}O$, M^+ at m/e 218; IR ($CHCl_3$) cm^{-1} 3610, 2925, 1460, 1380 and 999; PMR (δ $CDCl_3$) 1·90, 2·28, 2·33 (s, 3H each), 4·00 (d, 2H, J=7Hz), 5·47 (m, 1H, $W_{\frac{1}{2}}$=18), 6·83 (s, 2H).

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