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Neighbouring Group Participation in the Biogenesis of the Vinyl Bromide Moiety of Chamigrene Metabolites

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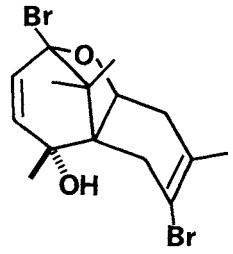
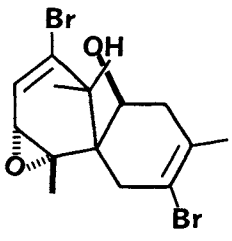
A neighbouring group promoted a biomimetic-type transformation of pacifenol into a bromo vinyl metabolite isolated from a red alga of Laurencia sp.

The marine sesquiterpene **1** was described[1] as the first example of a halogenated chamigrene metabolite with a vinyl bromide moiety, and prepacifenol **3** was envisaged[2] as its precursor, following the sequence **3** → **2** → **1**. Very recently, the postulated compound **2**, which was also considered[2] to be important in the biogenetic route for the secochamigrene[3] sesquiterpenes of genus Laurencia (red algae), has been found as a natural metabolite.[4]



1



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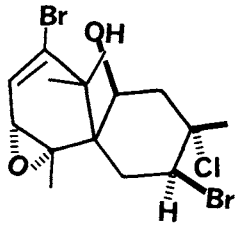
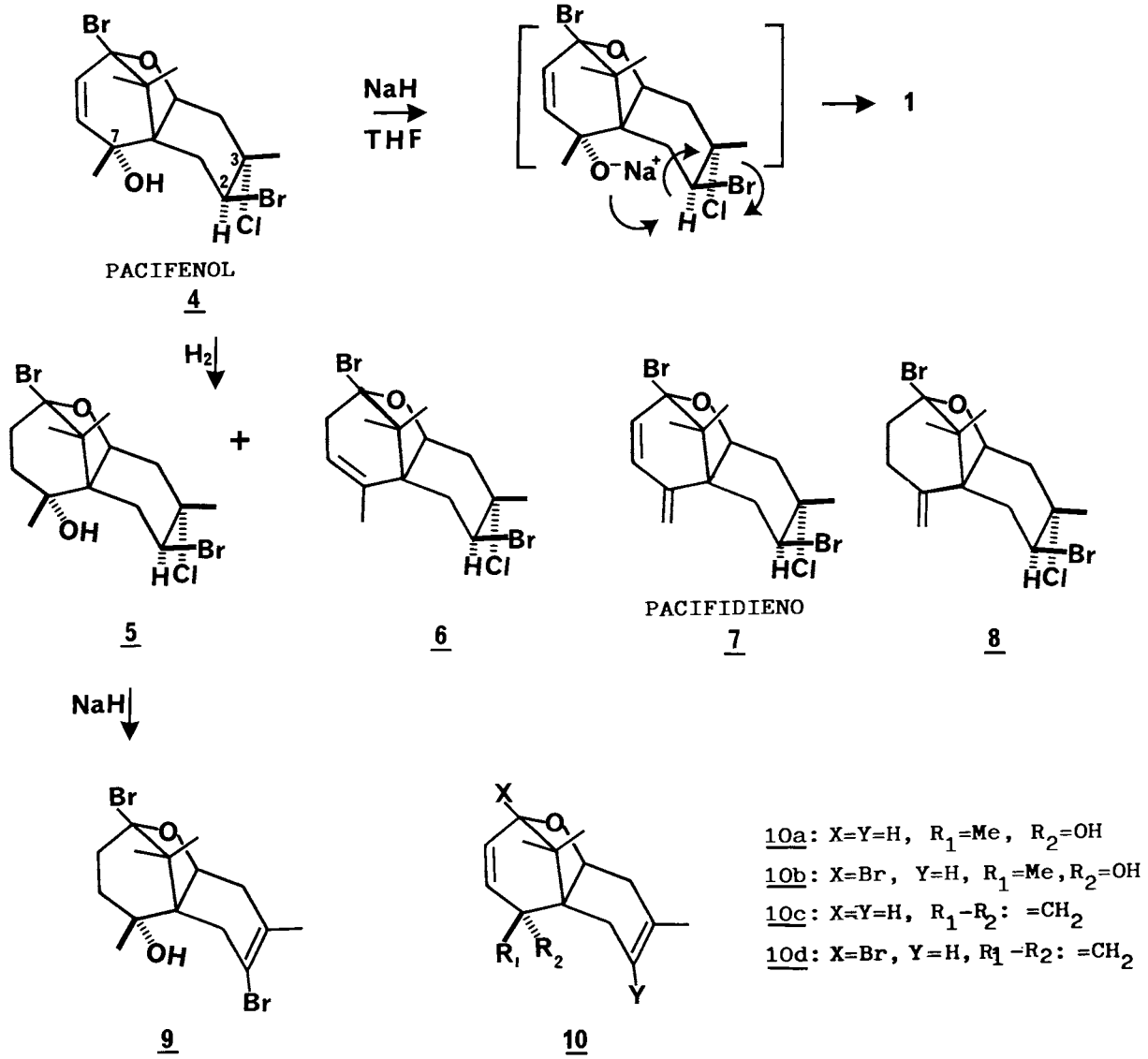


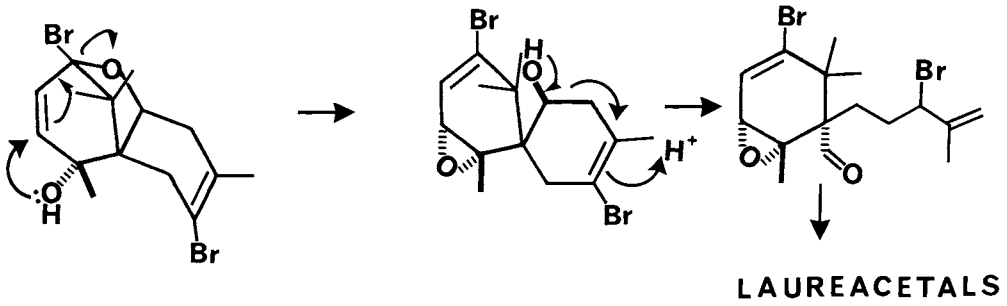
PREPACIFENOL

3

In this paper we report on chemical evidence supporting pacifenol **4** as the likely biogenetic precursor of **1**. Compound **1** is in essence the hydrogen chloride elimination product of pacifenol and, in fact, we found that the hydroxyl group of **4** mediated the elimination of HCl in a process that seems to mimic the biogenetic origin of the bromo vinyl function in chamigrenes.



Scheme 1.



Scheme 2.

When pacifenol[5] was treated with sodium hydride in THF at 20 °C, a clean reaction took place giving **1** quantitatively. Catalytic hydrogenation of **4** gave[6] mostly **5** and **6**. Compounds **4** and **5** were readily dehydrated[7] to pacifidiene **7**[5] and **8**, respectively. The hydrogenated alcohol derivative **5** also reacted with NaH to give the corresponding compound **9**[6] by loss of HCl, whereas the C-7 dehydroxy derivatives **6-8** were inert under the afore-mentioned conditions.

These results can be rationalized as follows: a) the boat conformation of ring B brings the alcohol and the α-hydrogen at C-2 close enough for the resulting alkoxide to assist a long-range syn-elimination of HCl with the neighbouring chloride at C-3, by the action of NaH; b) lacking the α-hydroxyl group at C-7, compounds **6-8** were unreactive towards NaH (Scheme 1).

Pacifenol and its dehydroxy derivative pacifidiene **7** react[8] with $n\text{-}Bu_3SnH$ to produce **10**a, **10**b and **10**c, **10**d, respectively, by elimination of both of the halogen systems at C-2,C-3 of ring B. Compound **10**b was identified[9] as a natural metabolite previously isolated from a Laurencia and the structure of **1** was readily characterized as being identical with the sesquiterpene isolated[1] from L. nipponica Yamada.

The 2,3-chlorobromo system of ring B of pacifenol is very common[10] in other marine sesquiterpenes isolated from Laurencia. It should thus be expected to find the corresponding dehydrohalo derivatives as natural products by spontaneous HCl-elimination. However, compounds **1** and **2** are the only reported structures formally derived by loss of HCl from pacifenol and prepacifenol, respectively, among the polyhalogenated marine sesquiterpenes, which is surprising.

The requisite of certain structural and functional features in the parent sesquiterpene to assist the elimination, according to the mechanism described, could be an explanation but, in this assumption, prepacifenol **3** cannot be the precursor of **2** because **3** has an epoxide at C-7 instead of a hydroxyl group. It is thus necessary to postulate pacifenol as the possible precursor of **2** via a S_N2'-type rearrangement of **1**, according to the sequence **4** → **1** → **2** → secochamigrenes as shown in Scheme 2.

The long-range assisted syn-elimination establishes a stereochemical relationship between three chiral centres that could be useful in the structural determination of this kind of marine metabolites.

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6) All new compounds gave satisfactory IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectral data.

7) By treatment with d,1-10-camphorsulfonic acid in benzene.

8) Products were dissolved in oxygen-free dry benzene, a catalytic amount of AIBN and 2 equiv. of n-Bu_3SnH at 20 °C.

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