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PREPACIFENOL EPOXIDE, A HALOGENATED SESQUITERPENE DIEPOXIDE

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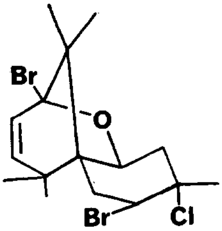
Our studies of the chemical constituents of the sea hare *Aplysia californica* have shown that the sea hare concentrates halogenated metabolites from its algal diet within the digestive gland.[1] In particular, specimens of *A. californica* collected intertidally at La Jolla contained pacifenol (1)[2] and johnstonol (2)[3], both metabolites of the red alga *Laurencia pacifica*, as major constituents of the digestive gland. We have recently isolated several related compounds as minor components of digestive gland extracts. We wish to report the isolation of prepacifenol epoxide (3) and its conversion to johnstonol (2) and to the diol 5.

Repeated silica gel chromatography of the ether soluble material from the digestive glands of *Aplysia* yielded prepacifenol epoxide (3): mp 98-9° (1% of ether soluble material). The high resolution mass measurement ($^m/e$ 442 = 441.9548; $C_{15}H_{21}O_3Br_2{}^{79}Cl^{35}$ requires $^m/e$ = 441.9547) indicated that 3 was an isomer of johnstonol (2). The nmr spectrum (220 MHz, $CDCl_3$, TMS) of 3 contained signals for four methyl groups at δ 0.95, 1.50, 1.54 and 1.86, two α-epoxy protons at 3.00 and 3.58, one proton α to bromine at 4.64 and one proton α to hydroxyl at 4.00 ppm. The presence of the hydroxyl group was indicated by a band at 3500 cm^{-1} in the infrared spectrum, together with a one proton signal at δ 1.96 in the nmr spectrum which disappeared on D_2O treatment. Further details of the stereochemistry of prepacifenol epoxide could be deduced from the coupling constants observed in the nmr spectrum. An absence of coupling between the two α-epoxy protons indicated that the vicinal epoxides were trans to one another. The coupling constants for the proton α to bromine (J = 13.5, 4.0 cps) and the proton α to hydroxyl (J = 3.5, 3.5 6 to -OH cps) suggested an equatorial bromine and an axial hydroxyl. All spectral data were



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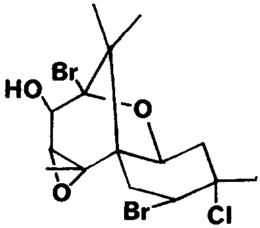

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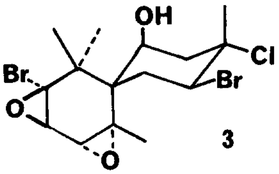

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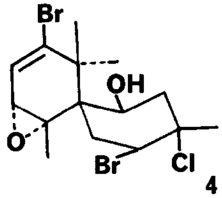

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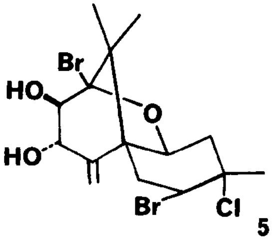

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therefore compatible with the structure shown as prepacifenol epoxide (3).

The structure of prepacifenol (4) had been confirmed by its conversion to pacifenol (1) under mild acid catalysis[4]. We therefore confirmed the structure of prepacifenol epoxide 3 by its conversion into johnstonol (2) in high yield by treatment with a catalytic quantity of oxalic acid in refluxing methanol for 24 hours. Under stronger acid conditions, namely p-toluenesulfonic acid in refluxing benzene, prepacifenol epoxide was converted into a diol 5[5], which had been obtained by Sims et al. by treatment of johnstonol (2) with hydrogen bromide in acetic acid[3]. The diol 5 has also been isolated as a minor component from the digestive gland of *A. californica*.

Our previous research had suggested that most of the compounds found in *Aplysia* could be located as algal metabolites. We therefore reexamined the red alga *Laurencia johnstonii*, from which johnstonol (2) had been isolated[3]. Extraction of air-dried material gave johnstonol (2) as the major metabolite, while ethyl acetate extraction of fresh material gave predominantly prepacifenol epoxide (3) (6.3% of ether solubles). Thus johnstonol (2) appears to be an artifact formed from prepacifenol epoxide (3) both during isolation from *L. johnstonii* and also in the digestive gland of the sea hare.

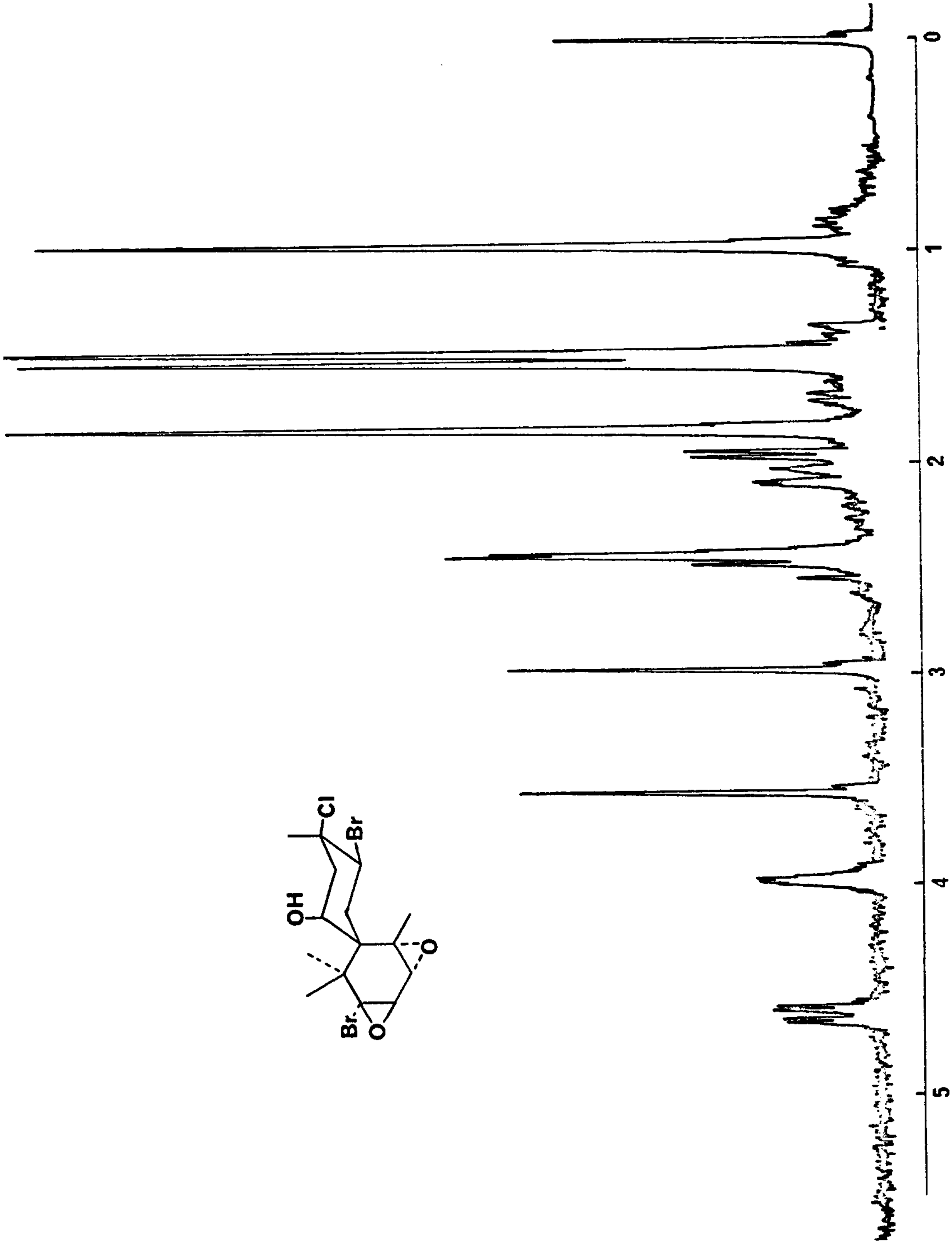

Figure. 220 MHz nmr spectrum of prepacifenol epoxide (3) in CCl_4.

Acknowledgement

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4. J. J. Sims, W. Fenical, R. M. Wing and P. Radlick, J. Amer. Chem. Soc. **95**, 972 (1973).
5. mp 172-3°; nmr ($CDCl_3$, TMS) δ 0.91 (s, 3H), 1.39 (s, 3H), 1.83 (s, 3H), 4.29 (s, 1H), 4.55 (dd, 1H), 4.79 (s, 1H), 5.07 (dd, 1H), 5.39 (s, 1H) and 5.58 (s, 1H).