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MARINE NATURAL PRODUCTS XIII.[1] ISOLATION AND SYNTHESIS OF SOME HALOGENATED KETONES FROM THE RED SEAWEED *DELISEA FIMBRIATA*.

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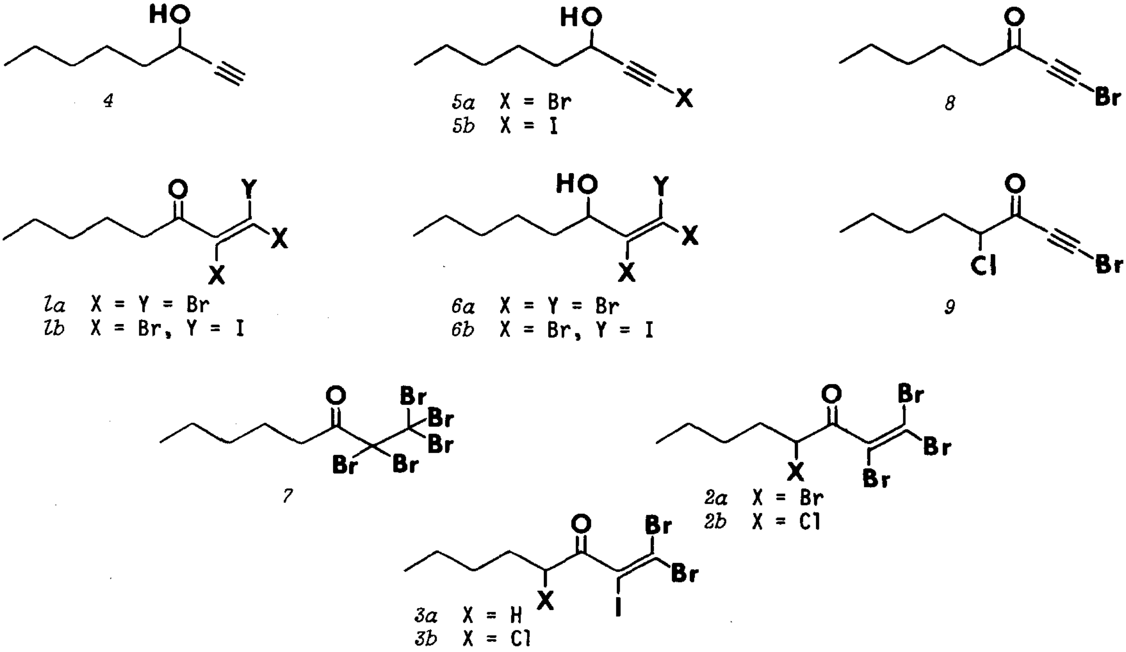
Our recent interest in the red alga *Delisea fimbriata* (Lamour.) (Bonnemaisoniaceae), stimulated by the absence of the usual epiphytic material, led to the isolation of a series of γ-lactones.[1] In addition we have now isolated a group of highly halogenated ketones *1a*, *2a*,*b* and *3a*,*b*, some of which show mild antifungal activity. Examination of the volatile constituents of the related alga *Ptilonia australasica* by Wells[2] has produced some related ketones.

Scheme 1.



4

5a X = Br
5b X = I

8

1a X = Y = Br
1b X = Br, Y = I

6a X = Y = Br
6b X = Br, Y = I

9

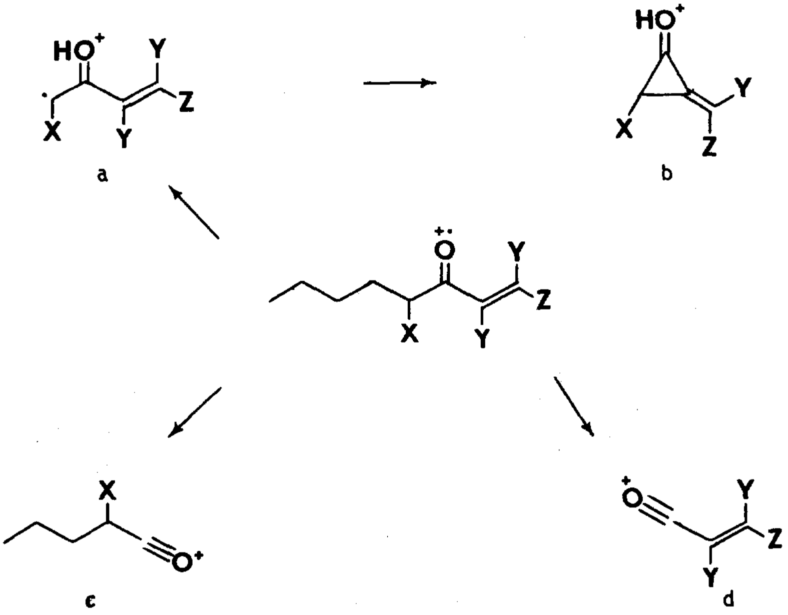
7

2a X = Br
2b X = Cl

3a X = H
3b X = Cl

The air dried alga was extracted with methylene chloride and the resulting oil subjected to open column silica gel chromatography. High pressure liquid chromatography (silica gel and C-18 reverse phase) of ketone containing fractions gave pure *1a* as the major metabolite (0.14% of dry weight). The infrared spectrum of *1a* contains carbonyl absorption at 1715 cm^{-1}. The proton nmr spectrum (60MHz, CCl_4, δ) shows a methylene adjacent to a carbonyl (2.73, 2H, J=6 Hz), an aliphatic envelope (1.9-1.1, 6H) and a methyl triplet (0.9, 3H, J=5 Hz). The ^{13}C nmr spectrum (WH-90, $CDCl_3$, ppm) suggests a ketone (196.8, s), a halogenated tetrasubstituted olefin (=CBr_2, 90.9, s; -CBr=, 121.8, s) and an n-pentyl chain (40.5, 30.9, 23.0, 22.2, t; 13.7, q). The mass spectrum exhibits a small molecular ion at m/e 360, the isotope cluster supporting a formula of $C_8H_{11}Br_3O$. Analysis of the mass spectral fragmentation pattern, Figure 1, shows the base peak at m/e 99 (ion c, X=H) and a small ion cluster at m/e 289 (ion d, Y=Z=Br) which result from cleavages alpha to the carbonyl and a McLafferty rearrangement ion at m/e 304, 306, 308, 310 (ion a, X=H, Y=Z=Br). These data support the structure of *1a* as a pentyl tribromovinyl ketone.

Figure 1. Mass Spectral Fragmentation Pattern.



However, the infrared band at 1715 cm^{-1} is at unusually high frequency for a normal, acyclic α,β-unsaturated ketone and suggests that the carbonyl and olefin are either in the s-cis conformation or are rotated out of coplanarity due to steric hindrance. IR spectral correlations from β-chlorovinyl ketones[3] predict an s-cis conformation for *1a*. If *1a* is predominantly in the s-cis conformation, then the calculated uv maximum should be 300 nm. However, the uv absorption of *1a* λ_{max} (methanol) 220 (ε=7000), 283 (ε=1080) is more consistent with two separate chromophores - 220 nm for $\pi \rightarrow \pi^*$ transition of the tribrominated olefin and 283 nm for carbonyl $n \rightarrow \pi^*$ transition. Hence, the uv data support the contention that steric hindrance in *1a* forces the carbonyl to be out of planarity with the olefin. In order to verify the contention of steric hindrance and prove the structures, we have synthesized compounds *1a,b* and *2a,b*.

The tribromoketone *1a* is prepared, Scheme 1, by treatment of commercially available *4* with aqueous potassium hypobromite[4] to yield *5a* (100%), which is brominated with bromine in carbon tetrachloride to give the tribromo alcohol *6a* (96%). Jones oxidation[5] of alcohol *6a* yields pure *1a* (91%), identical in all respects to the natural product.

Similarly, treatment of *4* with methanolic potassium hypoiodite[6] gives *5b* (quantitative yield) which is brominated with bromine in carbon tetrachloride to yield *6b* (83%), presumedly the E-isomer.[7] Jones oxidation of *6b* gives *1b* (55%). The mass spectral fragmentation pattern, Figure 1, of *1b* is *not* identical to the naturally occurring dibromoiodoketone. Hence, the structure of the natural product is assigned as *3*. The natural product, *3*, shows type b ions at m/e 225, 227, 229 (X=H, Y=Z=Br) which are absent in synthetic *1b*. Instead, *1b* exhibits type b ions at m/e 272, 274 (X=H, Y=Br, Z=I).

The 4-bromoketone *2a* is prepared in 69% yield by treatment of *1a* with pyridinium hydrobromide perbromide in glacial acetic acid. Interestingly, *2a* does not arise by a straightforward bromination of an enol intermediate but rather by decomposition of the pentabromoketone *7*. The proton nmr and mass spectral fragmentation patterns of natural and synthetic *2a* are identical.

All attempts to synthesize *2b* via α-chlorination of *1a* failed. However, treatment of bromoketone *8* with sulfuryl chloride in carbon tetrachloride yields *9* (32%). Bromination of *9* with bromine in carbon tetrachloride over potassium carbonate yields *2b* (46%), identical by mass spectral examination to the natural product.

Table 1 lists the ^{13}C nmr chemical shifts of ketones *1a*,*b* and *2a*,*b*.

Table 1. CMR Chemical Shifts, ppm (TMS=0), $CDCl_3$

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
1a	90.9	121.8	196.8	40.5	30.9	23.0	22.2	13.7
1b	55.6	128.5	197.0	40.6	31.0	23.0	22.3	13.8
2a	96.7	119.5	189.2	50.2	32.7	29.1	22.0	13.8
2b	94.9	119.1	190.9	60.8	33.1	28.0	22.0	13.8

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