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SYNTHESES OF MARINE OCHTODANE ANTIFEEDANTS VIA HYDROLYTIC DEHALOGENATION

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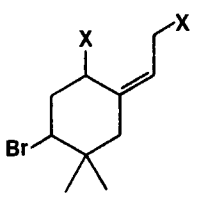
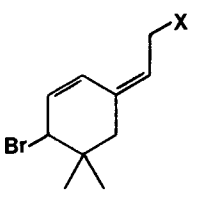
Summary: The syntheses of five naturally occurring antifeedants of the ochtodane ring system (1-ethyl-3,3-dimethylcyclohexane), previously isolated from the marine red alga Ochtodes crockeri, are reported. A key synthetic step involves the hydrolytic debromination of 6-bromo-1,4-ochtodien-3-ol.

Marine algae of the genera Ochtodes, Chondrococcus, and Plocamium (Rhodophyta) are well known for their production of polyhalogenated acyclic and cyclic monoterpenoids.[2] Natural products of the ochtodane ring system (1-ethyl-3,3-dimethylcyclohexane) are prevalent in Ochtodes and Chondrococcus and appear to serve as predation deterrents, many exhibiting antifeedant, sedative, and toxic activities against the common marine herbivorous fish Pomacentrus coeruleus.[3] While antimicrobial activities of marine ochtodane derivatives have also been reported,[4] this bioactive class of monoterpenoids is not restricted to the marine environment. The compounds 2(E)-ochtoden-1-al, 2(Z)-ochtoden-1-al, and 2(E)-ochtoden-1-ol in combination with grandisol are components of the sex attractant of the male boll weevil, Anthonomus grandis.[5] As part of our work associated with syntheses of bioactive halogenated marine natural products and related studies concerning their dehalogenation and rearrangement chemistry, we report the syntheses of several ochtodane natural products.

An examination of the structures of various ochtodane natural products suggested that many of these compounds may be related through hydrolytic dehalogenation reactions. For example, a likely synthetic and biosynthetic relationship between the generalized polyhalogenated ochtodanes 1 and 2 and the natural product 2(Z),4-ochtodien-1,6-diol (3) is hydrolysis. These transformations require hydrolytic (El) double bond formation (C-4, C-5) in 1 to give 2, followed by hydrolysis (S_N1) of the C-6 bromide and C-1 halide to yield 3.



1, X=Br or Cl



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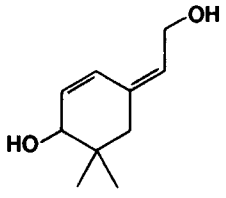

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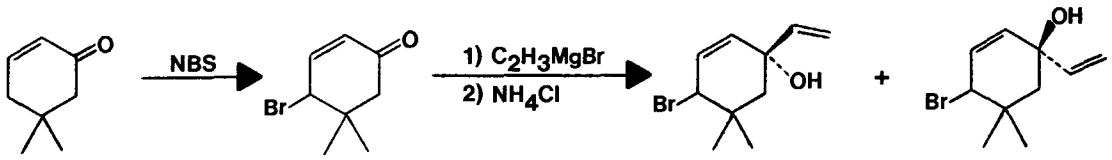
To test this proposal, we required a synthetic route which would provide suitable halogenated ochtodane derivatives. A common structural feature of many brominated marine terpenoids is the location of bromine alpha to a geminal dimethyl group in a substituted cyclohexane. This functionality is a result of the probable biosynthesis which involves bromonium ion-induced cyclization of acyclic polyenes. While such biomimetic cyclization reactions have been reported for the synthesis of brominated ochtodanes,[6] we chose an alternate route which provided a more facile approach to our synthetic targets. Our synthesis utilized free radical allylic bromination of a cyclic precursor rather than bromocyclization methods.

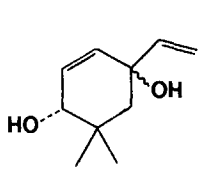


4 5 6 7

5,5-Dimethyl-2-cyclohexen-1-one (4) was prepared by reaction of dimedone (5,5-dimethyl-1,3-cyclohexadione) with $LiAlH_4$ followed by treatment with 10% aqueous H_2SO_4.[7] When 4 was treated with N-bromosuccinimide in refluxing CCl_4 for 10 minutes, 4-bromo-5,5-dimethyl-2-cyclohexen-1-one (5) was produced in 95% yield (80% from dimedone). Since 5 readily liberated HBr with the formation of 3,4-dimethylphenol, it was used immediately and without purification. The ochtodane ring system was readily assembled by treatment of 5 with vinylmagnesium bromide in diethyl ether at -78° for 20 minutes and the mixture was allowed to warm to 0° prior to the addition of saturated aqueous ammonium chloride. Separation of the reaction products by HPLC (12% ethylacetate-isooctane, μ-porasil) provided two isomers of racemic 6-bromo-1,4-ochtodien-3-ol (6 and 7, 45:55 ratio, 75% yield, 60% yield from dimedone). The structures of 6 and 7, including relative stereochemistry, were determined by ^1H and ^{13}C NMR[8] (for 6, 6(S*)-bromo-1,4-ochtodien-3(R*)-ol: ^1H NMR (100 MHz, $CDCl_3$) δ 6.08 (1H) dd, J=9.7, 5.2 Hz; 5.93 (1H) dd, J=17.2, 10.4 Hz; 5.53 (1H) d, J=9.7 Hz; 5.28 (1H) dd, J=17.2, 1.0 Hz; 5.10 (1H) dd, J=10.4, 1.0 Hz; 4.43 (1H) d, J=5.2 Hz; 2.06 (1H) d, J=14 Hz; 1.57 (1H) d, J=14 Hz; 1.25 (3H) s; 1.15 (3H) s; ^{13}C NMR (25 MHz, $CDCl_3$, PPM rel. to TMS) 144.8, 131.4, 130.1, 112.9, 71.2, 59.5, 44.7, 34.6, 30.3, 27.0; and for 7, 6(S*)-bromo-1,4-ochtodien-3(S*)-ol: ^1H NMR (100 MHz, $CDCl_3$) δ 6.03 (1H) dd, J=10.1, 3.4 Hz; 5.89 (1H) dd, J=17.4, 10.4 Hz; 5.57 (1H) d, J=10.1 Hz; 5.24 (1H) dd, J=17.4, 1.2 Hz; 5.09 (1H) dd, J=10.4, 1.2 Hz; 4.46 (1H) d, J=3.4 Hz; 2.00 (1H) d, J=14 Hz; 1.70 (1H) d, J=14 Hz; 1.20 (3H) s; 1.06 (3H) s; ^{13}C NMR (25 MHz, $CDCl_3$, PPM rel. to TMS) 144.5, 131.7, 131.2, 113.7, 71.0, 60.8, 46.9, 36.4, 28.6, 27.6).[12]

The ochtodane derivatives 6 and 7 have not been reported as natural products but represented good models for our investigations of hydrolytic dehalogenation reactions. When either 6 or 7 was subjected to conditions of hydrolysis (30% water-acetone, 25°, 8 hrs.), four isomeric diols were isolated (HPLC, 20% ethylacetate-isooctane, μ-Porasil): 1,4-ochtodien-3,6-diol (8), 2(Z),4-ochtodien-1,6-diol (3), 2(E),4-ochtodien-1,6-diol (9), and 1,3(4)-ochtodien-5,6-diol (10).[9] These isomeric diols were produced in a 2:5:5:1 ratio, respectively, (55% yield) and were found to be identical with authentic samples isolated from Ochtodes crockeri.[10] This reaction initially

involves hydrolysis (S_N1) of the C-6 bromide to yield 8 and HBr. The acidic conditions thus generated induce carbocation formation in compound 8 at the bis-allylic C-3 position. Compounds 8, 3, 9, and 10 are produced when the resonance-stabilized carbocation is trapped by water at C-1, C-3,



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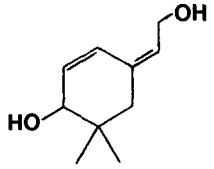

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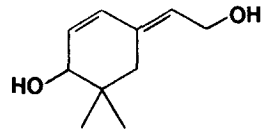

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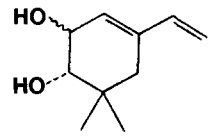

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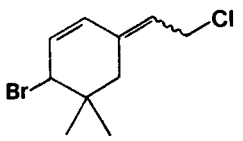
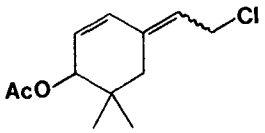
or C-5. These transformations support the proposal that hydrolytic dehalogenation may be utilized to convert polyhalogenated to polyoxygenated ochtodane derivatives in biosynthetic processes. These diols have been previously reported to elicit feeding inhibition behavior in the marine damselfish (Pomacentrus coeruleus).[3]

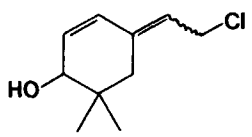
Another ochtodane antifeedant, 1-chloro-2(E),4-ochtodien-6-ol (16) was also synthesized from 6-bromo-1,4-ochtodien-3-ol (6 or 7). Treatment of 6 or 7 with thionyl chloride in diethyl ether provided 6-bromo-1-chloro-2,4-ochtodiene as a mixture of E and Z isomers (11 and 12, respectively).[11] These isomers were found to be resistant to conditions of hydrolysis but were readily decomposed on silica gel. When a mixture of 11 and 12 was treated with one equivalent of silver acetate in THF at 25°, the corresponding chloro-acetates 13 and 14 were produced. Basic hydrolysis (3% KOH-CH_3OH) of a mixture of 13 and 14 provided 1-chloro-2(E),4-ochtodien-6-ol (15) and 1-chloro-2(Z),4-ochtodien-6-ol (16). HPLC methods provided pure 15, which was identical with an authentic sample isolated from Ochtodes crockeri.



11=E
12=Z



13=E
14=Z



15=E
16=Z

To assess biological activities of new ochtodane derivatives, the epimeric alcohols 6 and 7 and a mixture of 11 and 12 were tested for antimicrobial and ichthyotoxic activities. The brominated alcohols 6 and 7 each exhibited moderate antibacterial activity (Staphylococcus aureus, agar plate method, 15 mm inhibition at 0.5 mg disc load); a mixture of 11 and 12 showed strong antibacterial activity (S. aureus, 20 mm inhibition at 0.5 mg disc load). Ichthyotoxicity (Pomacentrus coeruleus) was determined by the method reported by Paul et al.[3] A mixture of 11 and 12 was lethal to the damselfish at 15 µg/mL within one hour. Each of the brominated alcohols 6 and 7 produced immediate sedation at 20 µg/mL, but after 45 minutes the damselfish returned to apparent normal behavior. These differing bioactivities may be a function of a compound's propensity to undergo hydrolysis. The bromo-chloro-diene isomers 11 and 12 are resistant to hydrolysis, whereas the bromo-alcohols 6 and 7 readily hydrolyze, yielding non-toxic and non-sedative products (i.e., 8, 3, 9, and 10; see Reference 3). Such hydrolytic dehalogenation reactions of otherwise toxic polyhalogenated ochtodanes may serve as a natural detoxification process in the marine environment.

Acknowledgements

We wish to thank Matthew Beck for antibacterial testing and Lisa Heininger for ichthyotoxicity studies. We also acknowledge the Department of Chemistry, San Francisco State University, for its interest in our activities.

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8. All new compounds gave acceptable high resolution mass measurements.

9. Compound 10 was reported (reference 3) as 1,3(8)-ochtodien-5,6-diol but should be reassigned as 1,3(4)-ochtodien-5,6-diol based on its production from 6 and 7.

10. We wish to thank Dr. William Fenical for providing authentic samples of various Ochtodes natural products.

11. For 6-bromo-1-chloro-2(E),4-ochtodiene (12): ^{1}H NMR (100 MHz, $CDCl_3$) δ 6.10 (1H) d, J=10.1 Hz; 5.83 (1H) dd, J=9.8, 4.1 Hz; 5.69 (1H) t J=7.9 Hz; 4.38 (1H) d, J=4.1 Hz; 4.17 (2H) d, J=7.9 Hz; 2.49 (1H) d, J=15 Hz; 2.16 (1H) d, J=15 Hz; 1.09 (3H) s; 1.05 (3H) s.

12. Assignment of the C-3 relative stereochemistry in 6 and 7 are based on the chemical shifts of the C-8 methylene protons and $Eu(fod)_3$ shift studies.

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