Tetrahedron Vol. 43, No 6, pp. 1063 to 1070, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00
© 1987 Pergamon Journals Ltd

Unprecedented Constituents of a New Species of Acorn Worm

TATSUO HIGA*
Department of Marine Sciences, University of the Ryukyus
Nishihara, Okinawa 903-01, Japan

ROY K. OKUDA, R. MICHAEL SEVERNS, and PAUL J. SCHEUER*
Department of Chemistry, University of Hawaii at Manoa
Honolulu, Hawaii 96822

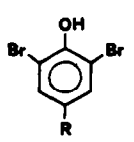
CUN-HENG HE, XU CHANGFU, and JON CLARDY*
Baker Laboratory, Department of Chemistry
Cornell University, Ithaca, New York 14853

(*Received in USA* 26 *January* 1987)

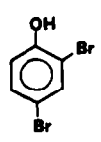
ABSTRACT. -- A new species of acorn worm, recently discovered in deep underwater caves off the island of Maui, yielded after chromatographic separation of the acetone extract the following secondary metabolites: (4S,5R,6S)-4-acetoxy-2,6-dibromo-5-hydroxy- cyclohex-2-enone (11), its C-6 epimer (12), (1R,4S,5R,6S)-4-acetoxy-2,6-dibromo-1,5-dihydroxy-cyclohexene (13), (4S,5R,6R)-4-acetoxy-2-bromo-5,6-epoxycyclohex-2-enone (14), its deacetyl derivative 15, and 2,4-dibromoresorcinol (9), in addition to phenols 1-4 and indole 10 as minor constituents. The structures of 11-15 were determined from spectroscopic data, and the absolute configurations by x-ray analysis of 11, 13, and 14. Although the species is morphologically related to the genus *Ptychodera*, the minor aromatic constituents are usually associated with the genus *Balanoglossus*. Epoxyenone 14 shows *in vitro* P388 activity with an IC_{50} of 10 ng/mL.

Acorn worms (Phylum Hemichordata, Order Enteropneusta) are inconspicuous, fragile marine invertebrates living in sand, mud, or under pebbles. Their habitat ranges from intertidal flats to considerable depths and from tropical to temperate waters. Many species have an odor reminiscent of iodoform (1) and some are bioluminescent (2). We were initially intrigued by the observation of the iodoform-like odor and studied the chemistry of five shallow-water species (3a-g). Characteristic metabolites are e.g. bromophenols 1-5, dimeric (6) and trimeric ethers of 5, halogenated indoles such as 7, and indigotin pigments (8) related to Tyrian purple (4). Dibromophenols 1 and 4 are responsible for the odor of some species of the genus *Balanoglossus* (3e,5), while 3-haloindoles (7) cause the odor of such species as *Ptychodera flava* (3a) and *Glossobalanus* sp.(3e) Other than deoxyribonucleosides isolated from the hydrophilic extract of *P. flava* (3g), more than twenty metabolites from lipophilic extracts of several species are halogenated aromatics. We have not encountered a single nonaromatic metabolite from common shallow-water species in Hawaii or Japan.

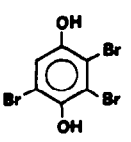
In September, 1983, one of us (RMS) discovered a new species of acorn worm from deep (-30m) underwater caves on the island of Maui. Morphological study by Hadfield indicated that it belonged to the genus *Ptychodera* (6). A single specimen was brought to our laboratory for chemical study; it was immediately placed in Me_2CO and kept in a freezer for about 50 days prior to isolation. To our surprise, the extract contained no detectable aromatic compounds but two nonaromatic metabolites (11,12) in a total yield of over ten percent of dry weight of the animal. From a larger recollection in 1984 we were able to isolate several related compounds and some aromatics. In this paper we describe their isolation and structural elucidation, including absolute stereochemistry by x-ray crystallography.



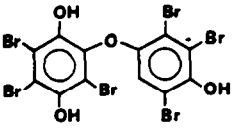
1 R = H
2 R = Br
3 R = OH



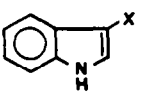
4



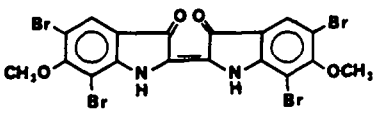
5



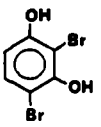
6



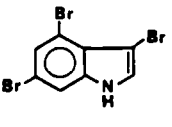
7 X = Cl, Br



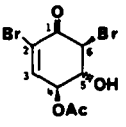
8



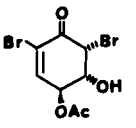
9



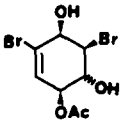
10



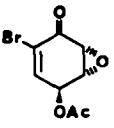
11



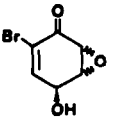
12



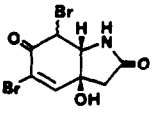
13



14



15

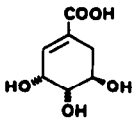


16

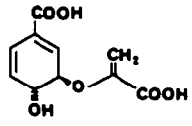
The animals (294 g) collected at Kinau Point, Maui by SCUBA were transported frozen to the laboratory and immediately extracted with Me_2CO. The CH_2Cl_2-soluble portion of the concentrated extract was chromatographed on silica gel. Further separation by hplc yielded phenols **1**–**4** and **9**, indole **10**, and cyclohexenone derivatives **11**–**15**. The phenols and compound **15** were minor constituents, while compounds **10**–**14** were abundant. Bromophenols **1** and **2** were obtained as a trace mixture. Comparison of the ^1H NMR and mass spectral data with those of authentic samples of **1** and **2** clearly indicated the presence of these compounds in the mixture. The phenols **3** and **4** and 3,4,6-tribromoindole (**10**) had been isolated previously from other species and were identified by spectral comparison. The last minor aromatic constituent was 2,4-dibromoresorcinol (**9**) as identified by EIMS and ^1H NMR data. The NMR signals were virtually identical with those reported for **9** (7). This is a new metabolite not encountered previously.

Compound **11** was obtained as a crystalline solid. Its formula, $C_8H_8Br_2O_4$, was established by high resolution EIMS. Spectral data indicated the presence of a hydroxyl (3430 cm^{-1}, D_2O exchangeable proton at δ 3.02), an acetoxy (1725 and 1218 cm^{-1}, 3H singlet at δ 2.18), and an enone chromophore (λ_{max} 255 nm, 1700 and 1607 cm^{-1}, a doublet at δ 7.22). Identical UV and Ir carbonyl absorptions with those of the cavernicolins (**16**) (8) suggested an α-bromocyclohexenone chromophore. Irradiation of the δ 7.22 doublet collapsed the doublet of doublets at δ 5.63 into a doublet (J = 8.2 Hz), thus placing the acetoxy group at C-4. Irradiation of the δ 5.63 signal changed the δ 7.22 doublet to a singlet and also a signal at δ 4.17 (ddd) to a doublet of doublets (J = 11.1, 2.7 Hz), thereby suggesting that the hydroxyl group is located at C-5. Irradiation of the δ 4.17 signal affected the resonances at δ 5.63, 4.68 (d, J = 11.1 Hz), and 3.02 (d, OH). The latter two signals became singlets. The doublet at δ 4.68 was assigned to a proton at C-6 which bears bromine. The large coupling constant between the protons at C-5 and C-6 requires them to be diaxial, which establishes diequatorial configuration for hydroxyl and bromine. The coupling constant (J = 8.2 Hz) between the protons at C-5 and C-4 suggests that H-4 is quasi-axial, and hence the acetoxy group quasi-equatorial. The absolute configuration of **11** was established by x-ray crystallographic analysis.

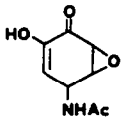
Compound **12** was assigned the same molecular formula, $C_8H_8Br_2O_4$, as **11** by high resolution mass measurement. Comparison of spectral data with those of **11** revealed **12** to be an epimer of **11**. The ^1H NMR spectra of **12** and **11** have identical signals. A striking difference is the



17



18

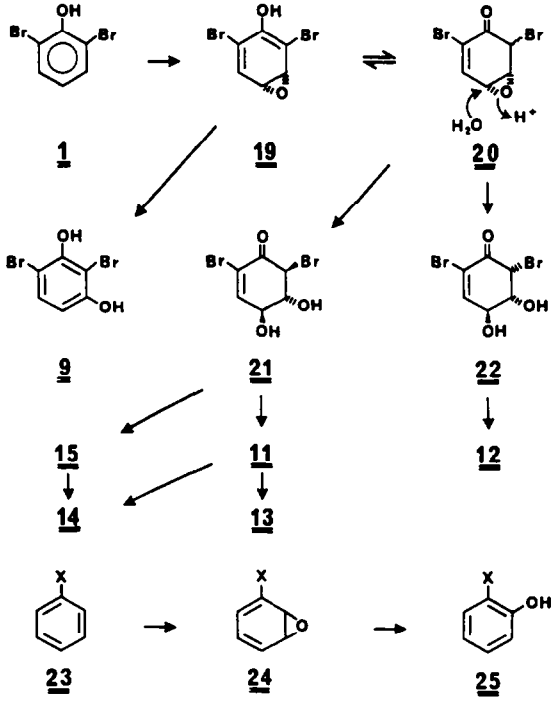


26

In compound 11 and 13 (both independent molecules) the cyclohexene ring is in the expected half chair conformation, i.e. atoms C-1 to C-4 are planar and atoms C-5 and C-6 are above and below this plane. In compound 14 the epoxide at the C-5,C-6 position flattens the entire ring. All of the ring torsional angles in 14 are small. The bond distances and angles for all of the compounds agree well with generally accepted values.

The results revealed that the configurations at the chiral centers C-4 and C-5 of all three compounds are the same and opposite to those of corresponding carbons in shikimic (17) and chorismic (18) acids (9). We therefore conclude that these cyclohexenones are not intermediates in the formation of phenols, but instead are products derived from the phenols. In a previous paper (3e) we proposed biogenetic schemes for the formation of the halogenated phenols and indoles from tyrosine and phenylalanine. Recently Tymiak and Rinehart (10) have shown by administering labeled precursors to the sponge *Aplysina fistularis* that some bromophenols closely related to 1-3 were indeed derived from tyrosine and phenylalanine. To account for the further degradation of some phenols to the cyclohexenones in the new species of acorn worm, a plausible mechanism is shown in Scheme 1. Enzyme-catalyzed oxidation of 2,6-dibromophenol (1) would lead to an arene oxide 19 which would be in equilibrium with the keto tautomer 20. Of the three possible arene oxides of 1, 19 is expected to be the predominant product, since it is consistent with the observed regioselectivity in the enzyme-catalyzed epoxidation of halobenzene (23) (11). Hydration of epoxide 20 should form the epimers 21 and 22, from which all the observed cyclohexenones could be derived. Although we were at first puzzled by finding resorcinol 9, for such meta-disposed polyphenols normally originate from an acetate pathway, its formation can be nicely explained through epoxide 19 in full analogy with observed preferential ortho-hydroxylation of halobenzene 23 via epoxide 24 (11).

Scheme 1



The aromatic constituents (1-4, 10) of the new *Ptychodera* species are intriguing from a taxonomic point of view. As described earlier, the odoriferous compounds 1 and 4 were previously observed only in the genus *Balanoglossus* (3e,5). Indole 10 was a minor constituent of *B. carnosus* only (3e). Hydroquinone 3 was found in *Glossobalanus* sp. and *B. misakiensis*, but not in the genus *Ptychodera* (3e). The phenol 2 was obtained from species in all the three genera *Ptychodera*, *Glossobalanus*, and *Balanoglossus* (3e). Although the new species is morphologically related to the genus *Ptychodera*, chemically it is more closely related to the genus *Balanoglossus* than to the other genera of Enteropneusta.

Cyclohexenones 11 and 12 showed feeding deterrent properties against the omnivorous fish *Tilapia mossambica* at a level of 10 μg/mg of feed. *In vitro* antitumor testing of compounds 11, 13, and 14 against P388 cells showed them to be active. Epoxide 14 was most active with an IC_{50} of 10 ng/mL. A structurally related cyclohexenone epoxide, antibiotic 26, isolated from *Streptomyces* sp., also has antitumor activity (12).

EXPERIMENTAL

Infrared spectra were measured as KBr pellets on a Hitachi 260-10 Infrared Spectrophotometer; UV spectra on a Cary 14 spectrophotometer; optical rotations on an Atago AA-5 Digital Polarimeter or Rudolph Research Autopol II Polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Nicolet NT-300, and mass spectra on a Varian MAT-311 mass spectrometer.

Collection, Extraction, and Isolation

The acorn worms (wet weight with ingested silt 294 g, dry weight after extraction 49 g) were collected in underwater caves at -30 m at Kinau Point, Maui. The sample was kept in a freezer overnight, transported to the laboratory, and immediately homogenized with Me_2CO in a mortar. The Me_2CO extract (800 mL) was concentrated, and the resulting aqueous suspension was extracted with CH_2Cl_2 (3 x 100 mL) to give 740 mg of oily residue. The residue was initially separated on a silica gel (25 g) column (EtOAc, 2:1) into 15 fractions, 20 mL each. Each of the fractions 1-12 was purified by hplc (Whatman Partisil M9 50/10 column) by eluting with 4:1 to 2:1 EtOAc; the remaining trace fractions were discarded. Eluates giving the same hplc peaks from each fraction were combined and chromatographed again on the same hplc system to yield, in order of increasing retention time, a mixture of 1 and 2 (1.3 mg), 4 (13.2 mg), 3 (10 mg), 9 (0.7 mg), 10 (30.4 mg), 14 (56.2 mg), 11 (19 mg), 13 (24.1 mg), 15 (0.6 mg), and 12 (67.6 mg).

2,6-Dibromophenol (1) and 2,4,6-Tribromophenol (2)

An odoriferous material (1.3 mg) was shown to be a mixture of 1 and 2 by EIMS [1: m/z 254, 252, 250 (M^+); 2: m/z 334, 332, 330, 328 (M^+)] and ^1H NMR [$CDCl_3$, 1: δ 7.42 (2H, d, J = 8.4 Hz), 6.68 (1H, t, J = 8.4 Hz); 2: δ 7.58 (s)] which were identical with those of authentic samples of 1 and 2 (3e).

2,4-Dibromophenol (4)

Purification of an HPLC-separated sample by sublimation gave a crystalline solid with a characteristic odor, mp 33.5-34.5°C. ^1H NMR [$CDCl_3$, δ 7.59 (1H, d), 7.30 (1H, dd), and 6.89 (1H, d)] and ir spectra were identical with those of an authentic sample of 4 (3e).

2,6-Dibromohydroquinone (3)

Recrystallization from $CHCl_3$ gave 3 as colorless needles, mp 168-169°C. The ^1H NMR [$CDCl_3$, δ 7.00(s)] and IR spectra were identical with those of an authentic sample of 3 (3e).

2,4-Dibromoresorcinol (9)

EIMS: m/z 270, 268, 266 (M^+), 252, 250, 248, 224, 222, 220, 161, 159, 157, 143, and 141; ^1H NMR ($CDCl_3$): δ 7.32 (1H, d, J = 8.4 Hz), 6.56 (1H, d, J = 8.4 Hz), 5.87 (1H, s, OH), and 5.59 (1H, s, OH). The NMR data were identical with those reported for this compound (7).

3,4,6-Tribromoindole (10)

Recrystallization from C_6H_6 gave slightly colored crystals, mp 90°C (dec.) The ^1H NMR spectrum in $CDCl_3$ [δ 8.40 (1H, br s), 7.47 (1H, d, J = 1.5 Hz), 7.45 (1H, d, J = 1.5 Hz), 7.24 (1H, d, J = 2.5 Hz)] and in Me_2CO-d_6 [δ 7.71 (1H, br s), 7.58 (1H, br s), and 7.42 (1H, brs)] were identical with those reported previously for 10 (3e). Acetylation with Ac_2O and pyridine at room temperature for 3 h gave 1-acetyl-3,4,6-tribromoindole, mp 175-180°C (dec); ^1H NMR ($CDCl_3$): δ 8.66 (1H, d, J = 1.5 Hz), 7.63 (1H, d, J = 1.5 Hz), 7.50 (1H, s), and 2.55 (3H, s).

(4S,5R,6S)-4-Acetoxy-2,6-dibromo-5-hydroxycyclohex-2-enone (11)

Recrystallization from hexane-EtOAc gave colorless crystals, mp 136-138°C; $[\alpha]_D^{25}$ +109.7° (c 1.24, $CHCl_3$); UV λ_{max} (MeOH): 255 (ε 5200); IR (KBr): 3430, 2920, 1725, 1700, 1607, 1218, and 1043 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.22 (1H, d, J = 2.4 Hz), 5.63 (1H, dd, J = 8.2, 2.4 Hz), 4.67 (1H, d, J = 11.1 Hz), 4.17 (1H, ddd, J = 11.1, 8.2, 2.7 Hz), 3.02 (1H, d, J = 2.7 Hz, D_2O exchangeable), and 2.18 (3H, s); ^{13}C NMR ($CDCl_3$): δ 146.0 (C-3), 122.7 (C-2), 74.6 (C-4), 72.7 (C-5), 56.7 (C-6), and 20.8 (CH_3); EIMS: m/z 330, 328, 326 (M^+), 288, 286, 284 ($M-C_2H_2O$), 270, 268, 266 ($M-C_2H_2O$, $-H_2O$), 249, 247 (M-Br), 231, 229 (M-Br, $-H_2O$), 207, 205 (M-Br, $-C_2H_2O$), 206, 204 (M-Br, $-C_2H_3O$), 189, 187 (M-Br, $-C_2H_2O$, $-H_2O$), 164, 162, 158, 126, 97, 53, 51, and 43 (base); HREIMS: m/z 325.8823; $C_8H_8{}^{79}Br_2O_4$ requires 325.8789.

(4S,5R,6R)-4-Acetoxy-2,6-dibromo-5-hydroxycyclohex-2-enone (12)

$[\alpha]_D^{23}$ +130° (c 0.1, CH_2Cl_2); UV λ_{max} (MeOH): 256 (ε 5500), 202 nm (ε 4200); IR (KBr): 3430, 2920, 1720, 1700, 1605, 1370, 1215, 1090, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.18 (1H, d, J = 2.7 Hz), 5.61 (1H, dd, J = 7.4, 2.7 Hz), 4.77 (1H, d, J = 3.5 Hz), 4.06 (1H, br dd, J = 7.4, 3.5 Hz), 2.88 (1H, br s, D_2O exchangeable), and 2.18 (3H, s); ^{13}C NMR ($CDCl_3$): δ 145.2 (C-3), 72.7 (C-5), 71.6 (C-4), 52.3 (C-6), and 20.8 (CH3); EIMS: m/z 330, 328, 326 (M^+), 288, 286, 284, 270, 268, 266, 249, 247, 231, 229, 207, 205, 189, 187, 164, 162, 161, 159, 126, 125, 97, 53, 51, and 43 (base); HREIMS: m/z 325.8823; $C_8H_8Br_2O_4$ requires 325.8789.

(1R,4S,5R,6S)-4-Acetoxy-2,6-dibromo-1,5-dihydroxycyclohexene (13)

Recrystallization from hexane-EtOAc gave colorless crystals, mp 150.5-151.5°C; IR (KBr): 3420, 1720, 1365, 1285, 1240, 1105, 1080, 1045, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.10 (1H, d, J = 2.7 Hz), 5.27 (1H, dd, J = 7.0, 2.7 Hz), 4.47 (1H, dd, J = 3.4, 3.3 Hz), 4.25 (1H, dd, J = 11.4, 3.3 Hz), 4.17 (1H, dd, J = 11.3, 7.1 Hz), 2.77 (1H, d, J = 3.7 Hz), 2.64 (1H, br s), and 2.11 (3H, s); CIMS: m/z 333 (8), 331 (15.4), 329 (M^+ + 1) (7.8), 315 (4.6), 313 (9.5), 311 (5.3), 273 (5), 271 (10), 269 (5.5), 255 (23.7), 253 (49.9), 251 (28), 227 (16.8), 225 (32.2), 223 (16.8), 191 (40.6), 189 (37.8), 175 (57.2), 173 (61.3), and 111 (100 rel. %); EIMS: m/z 233 (29), 231 (29), 208 (19), 206 (20), 191 (99), 189 (96), 166 (52), 154 (52), 110 (100), 109 (62), 82 (20), 80 (15), and 43 (94 ref. %); HREIMS: m/z 232.9624; $C_8H_8{}^{81}BrO_3$ requires m/z 232.9636; 205.9590; $C_6H_7{}^{79}BrO_3$ requires m/z 205.9579, and m/z 190.9523; $C_6H_6{}^{81}BrO_2$ requires 190.9531.

(4S,5R,6R)-4-Acetoxy-2-bromo-5,6-epoxycyclohex-2-enone (14)

Recrystallization from hexane-EtOAc acetate gave colorless needles, mp 93-94°C; $[\alpha]_D^{19}$ +265° (c 0.12, $CHCl_3$); IR (KBr): 1730, 1700, 1615, 1375, 1240, 1210, 1030, 970, 910, 780 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.04 (1H, dd, J = 5.3, 2.3 Hz), 5.73 (1H, dt, J = 5.3, 1.3 Hz), 3.75 (1H, ddd, J = 3.4, 2.3, 1.3 Hz), 3.68 (1H, dd, J = 3.4, 1.2 Hz), and 2.13 (3H, s); EIMS: m/z 248 (2.7), 246 (M^+, 3.9), 206 (25), 204 (25), 190 (3.7), 188 (3.4), 178 (11), 176 (11), 177 (15.4), 175 (15.9), 161 (11.3), 159 (12.8), 133 (12.3), 131 (13.7), 125 (13.2), 107 (10.1), 97 (33.3), 43 (100 ref. %); HREIMS: m/z 245.9542; $C_8H_7{}^{79}BrO_4$ requires 245.9528.

(4S,5R,6R)-2-Bromo-5,6-epoxy-4-hydroxycyclohex-2-enone (15)

Recrystallization from hexane-$CHCl_3$ gave colorless crystals, mp 123-127°C; $[\alpha]_D^{22}$ +220°C (c 0.09, CHCl3); ^1H NMR (CDCl3): δ 7.14 (1H, dd, J = 5.0, 2.4 Hz), 4.76 (1H, tdd, J = 8.6, 5.1, 1.2 Hz), 3.84 (1H, ddd, J = 3.6, 2.4, 1.2 Hz), 3.69 (1H, dd, J = 3.6, 1.1 Hz), and 2.29 (1H, d, J = 8.6 Hz, D_2O exchangeable). Acetylation (Ac_2O/pyridine, 15 min, room temperature) gave a sample identical with 14 in TLC and ^1H NMR data.

Single crystal x-ray diffraction analysis of 13

Preliminary x-ray photographs displayed orthorhombic symmetry. Accurate cell constants of a = 5.332(2), b = 11.476(4), and c = 17.773(6) Å were determined from a least-squares fit of fifteen moderate 2θ-values. Systematic extinctions and a crystal density of 2.0 g/cc were uniquely consistent with space group $P2_12_12_1$ with one molecule of composition $C_8H_{10}Br_2O$ forming the asymmetric unit. All unique diffraction maxima with 2θ < 114° were collected on a computer controlled four-circle diffractometer using graphite monochromated Cu Kα-radiation (1.54178 Å). Of the 920 unique reflections collected in this fashion, 884 (96%) were judged

observed and used in all subsequent calculations (13). A phasing model was easily found using bromine positions deduced from the Patterson synthesis. Block diagonal least squares refinements were followed by a ΔF-synthesis to locate hydrogens. Final refinement was done using the program CRYSTALS. The final model had anisotropic nonhydrogen atoms, damped isotropic hydrogens, and anomalous scattering corrections for the bromines. The model shown refined to a conventional crystallographic residual of 0.0819 and the enantiomer refined to a residual of 0.0849, a statistically significant difference (14).

Compounds 11 and 14 were analyzed in an identical fashion. Compound 14 crystallized in the orthorhombic space group $P2_12_12_1$ with a = 8.114(1), b = 7.886(1), and c = 14.236(2) Å with one molecule of composition $C_8H_7BrO_4$ forming the asymmetric unit. Of the 811 unique reflections measured, 733 (90%) were judged observed. The final agreement factors were 0.0646 for the stereoisomer shown and 0.0688 for the enantiomer.

Compounds 11 crystallized in the monoclinic space group $P2_1$ with a = 8.901(1), b = 9.745(1), c = 12.142(1) Å and β = 90.84° and two molecules of $C_8H_8Br_2O_4$ formed the asymmetric unit. A total of 1498 (99%) of the 1511 measured reflections were judged observed. The final residual were 0.0592 for the stereoisomer shown and 0.0605 for the enantiomer. Both independent molecules in the asymmetric unit had the same absolute configuration and essentially the same conformation.

Acknowledgments

We wish to thank Shinichi Sakemi for technical assistance, Lars Bergknut for measuring mass spectra, Dr. Deborah Roll for CIMS, Drs. Steve Coval, William Baker, and Bulent Terem for determining some of the NMR spectra. We also thank Professor G. Snatzke for carrying out the CD measurement TH acknowledges partial financial support from Harbor Branch/SeaPharm and from University of Hawaii Foundation. We are grateful for financial support from the National Science Foundation and from the University of Hawaii Sea Grant College Program under Institutional Grant NA 81AA-D-0070 from NOAA, Office of Sea Grant, U.S. Department of Commerce. The Cornell authors wish to thank the New York State Sea Grant, NSF INT4133 and NIH CA24487 for financial support.

LITERATURE CITED

1. L. H. Hyman, "The Invertebrates," MacGraw-Hill, New York, 1959, Vol. 5, p. 143.
2. L. S. Dure and M. J. Cormier, *J. Biol. Chem.*, 239, 2351 (1964).
3. (a) T. Higa and P. J. Scheuer, *Naturwissenschaften*, 62, 395 (1975). (b) T. Higa and P. J. Scheuer, *Heterocycles*, 4, 227 (1976). (c) *ibid.*, 231. (d) T. Higa and P. J. Scheuer in "Marine Natural Products Chemistry," Ed. by D. J. Faulkner and W. H. Fenical, Plenum Press, New York, 1977, pp. 35-43. (e) T. Higa, T. Fujiyama, and P. J. Scheuer, *Comp. Biochem. Physiol.*, 65B, 525 (1980). (f) T. Higa, T. Ichiba, and R. K. Okuda, *Experientia*, 82B, 107, (1985). (g) S. Sakemi, and Higa T., *Comp. Biochem. Physiol.*, 82B, 107 (1985).
4. C. Christophersen. In "Marine Natural Products, Chemical and Biological Perspectives," Ed. by P. J. Scheuer, vol. 5, Academic Press, New York, 1983, p. 295.
5. R. B. Ashworth and M. J. Cormier, *Science*, 155, 1558 (1967).
6. M. G. Hadfield, personal communication.
7. A. G. Howard, R. A. Pizzie and J. W. Whitehouse, *Water Res.*, 18, 735 (1984).
8. M. D'Ambrosio, A. Guerriero, P. Traldi, and F. Pietra, *Tetrahedron Lett.*, 23, 4403 (1982); A. Guerriero, M. D'Ambrosio, P. Traldi, and F. Pietra, *Naturwissenschaften*, 71, 425 (1984).
9. T. A. Geissman and D. H. G. Crout, "Organic Chemistry of Secondary Plant Metabolites," Freeman-Cooper, San Francisco, 1969, p. 137.
10. A. A. Tymiak and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, 103, 6763 (1981).
11. B. J. Auret, S. K. Balani, D. R. Boyd, R. M. Greene, and G. A. Berchtold, *J. Chem. Soc. Perkin Trans. I*, 2659 (1984).
12. M. D. Lee, A. H. Fantini, G. O. Morton, J. C. James, D. B. Borders, and R. T. Testa, *J. Antibiot.*, 37, 1149 (1984).

13. All crystallographic calculations were done on a PRIME 9950 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 80, and RANTAN 80, systems of computer programs for the automatic solution of crystal structures from x-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, University of York, England, 1980; BLS78A, an anisotropic block diagonal least squares refinement written by K. Hirotsu and F. Arnold, Cornell University, 1980; CRYSTALS, a crystallographic system written by D. J. Watkin and J. R. Carruthers, Chemical Crystallographic Laboratory, University of Oxford, 1981; PLUTO78, a locally modified crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu and G. Van Duyne, Cornell University, 1985.

14. W. C. Hamilton, *Acta Crystallographica*, **18**, 502 (1965).

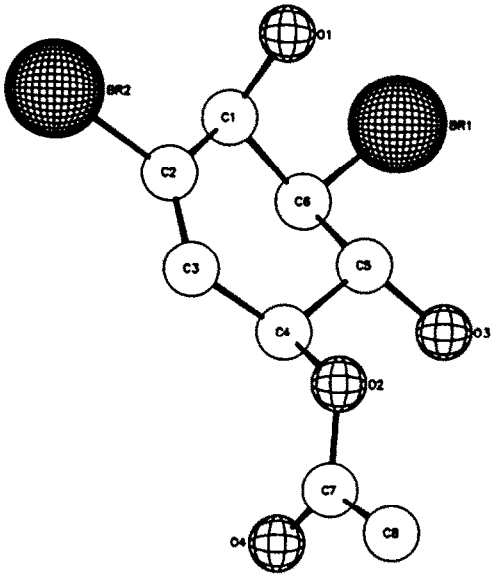


Fig. 1. PLUTO Drawing of (4S,5R,6S)-4-acetoxy-2,6-dibromo-5-hydroxycyclohex-2-enone (**11**).

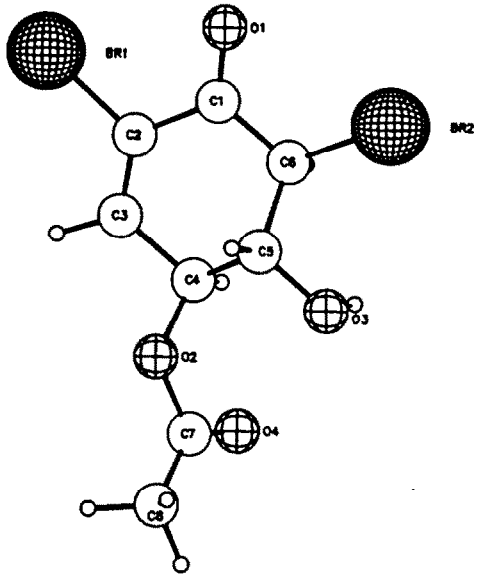


Fig. 2. PLUTO Drawing of (1R,4S,5R,6S)-4-acetoxy-2,6-dibromo-1,5-dihydroxy-cyclohexene (**13**).

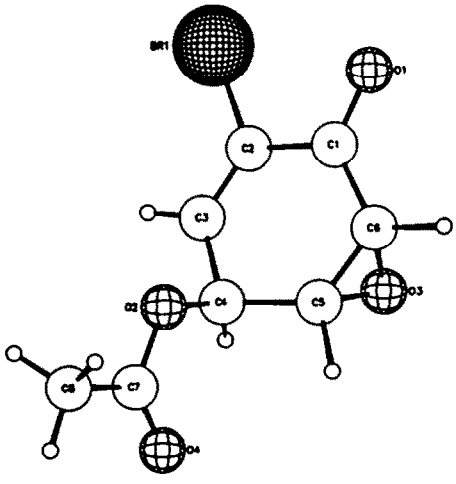


Fig. 3. PLUTO Drawing of (4S,5R,6S)-4-Acetoxy-2-bromo-5,6-epoxycyclohex-2-enone (**14**).