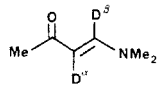
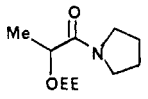
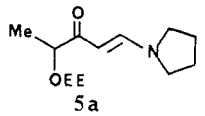
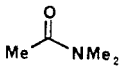
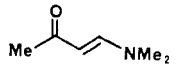
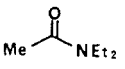
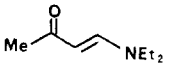
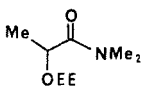
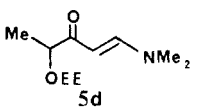
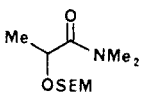
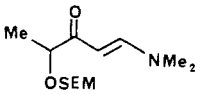
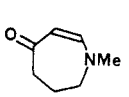
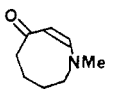
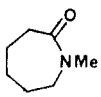
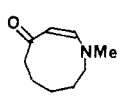


Figure 1.

Table I[a]

entry	reactants	products[b]	method[c]	yield, %
1	 3a	 5a	A	82
2	 3b	 5b	A	68
3	 3c	 5c	A[d], B[e]	
4	 3d	 5d	A	78
5	 3e	 5e	A	80
6	 3f	 5f	B	70
7	 3g	 5g	B	42
8	 3h	 5h	B	28

[a] EE = $CH(CH_3)OCH_2CH_3$, SEM = $CH_2OCH_2CH_2Si(CH_3)_3$. [b] Geometry of the double bond is determined as depicted on the basis of the coupling constant. [c] Method A: 2/THF. Method B: 2-BF_3·OEt_2/THF–hexane (v/v 1/5) (see Experimental Section). [d] No reaction. [e] Complex mixture of products formed.

using Wako silica gel B-5F. Tetrahydrofuran (THF) was distilled from benzophenone ketyl immediately before use. Amides **3b, c** and lactams **3f–h** were obtained from commercial sources; the amides **3a, d, e** were prepared from ethyl lactate by aminolysis and subsequent protection.

Preparation of 5a (Method A). To a solution of 1 (284 mg, 1.0 mmol) in THF (2 mL) was added *n*-BuLi (1.5 M hexane; 0.67 mL) at −78 °C, and the mixture was stirred for 15 min. Amide **3a** (172 mg, 0.8 mmol) in THF (2 mL) was then added to the mixture, and stirring was continued for 5 h at −45 °C. After MeOH was added, the reaction mixture was gradually warmed to room temperature and evaporated. The resulting oily residue was chromatographed on silica gel TLC (hexane/acetone, 50/50) to afford enaminone **5a** (158 mg, 82%) as a colorless oil: ^1H NMR (CCl_4) δ 1.0–1.5 (m, 9 H), 1.65–2.3 (m, 4 H), 3.1–4.05 (m, 7 H), 4.4–4.7 (m, 1 H), 5.1 (d, 0.6 H, J = 13.5 Hz), 5.2 (d, 0.4 H, J = 13.5 Hz), 7.6 (d, 1 H, J = 13.5 Hz); IR (neat) 1645 cm^{-1}; HRMS, m/z 241.1651, calcd for $C_{13}H_{23}NO_3$ 241.1675.

Enaminones **5b, d, e** were prepared in essentially the same manner as described above and their physical properties are listed below.

5b: oil; ^1H NMR (CCl_4) δ 1.9 (s, 3 H), 2.85 (s, 6 H), 4.85 (d, 1 H, J = 13.5 Hz), 7.25 (d, 1 H, J = 13.5 Hz); IR (neat) 1660 cm^{-1}; HRMS, m/z 113.0846, calcd for $C_6H_{11}NO$ 113.0840.

5d: oil; ^1H NMR (CCl_4) δ 1.0–1.4 (m, 9 H), 2.95 (s, 6 H), 3.25–3.65 (m, 2 H), 3.65–4.05 (m, 1 H), 4.4–4.75 (m, 1 H), 5.15 (d, 0.6 H, J = 13.5 Hz), 5.3 (d, 0.4 H, J = 13.5 Hz), 7.4 (d, 0.4 H, J = 13.5 Hz), 7.45 (d, 0.6 H, J = 13.5 Hz); IR (neat) 1655 cm^{-1}; HRMS, m/z 215.1516, calcd for $C_{11}H_{21}NO_3$ 215.1519.

5e: oil; ^1H NMR (CCl_4) δ 0.0 (s, 9 H), 0.6–1.0 (m, 2 H), 1.2 (d, 3 H, J = 6 Hz), 2.9 (br s, 6 H), 3.35–3.6 (m, 2 H), 3.8 (q, 1 H, J = 6 Hz), 4.45 (d, 1 H, J = 9 Hz), 4.55 (d, 1 H, J = 9 Hz), 5.2 (d, 1 H, J = 13.5 Hz), 7.35 (d, 1 H, J = 13.5 Hz); IR (neat) 1655 cm^{-1}; HRMS, m/z 273.1772, calcd for $C_{13}H_{27}NO_3$ 273.1759.

Preparation of 5f (Method B). To a THF (2 mL) solution of $LiC{\equiv}CSiPh_3$ (**2**) (1.0 mmol), prepared in the same manner as described in method A, was added BF_3·OEt_2 (142 mg, 1.0 mmol) in THF (0.5 mL), and the mixture was diluted with hexane (12.5 mL). To this solution was then added amide **3f** (79 mg, 0.8 mmol) in THF–hexane (1/5 v/v; 1 mL), and the mixture was stirred for 5 h at −45 °C. The reaction was quenched with 50% aqueous CH_3COOH (0.5 mL)[11] and gradually warmed up to room temperature. Solvents were evaporated in vacuo, and the residue was chromatographed on silica gel TLC (EtOH/acetone, 50/50) to afford **5f** as white solids: mp 81.5–82 °C; ^1H NMR ($CDCl_3$) δ 1.9–2.25 (m, 2 H), 2.9 (s, 3 H), 3.15 (t, 2 H, J = 7.5 Hz), 3.6 (t, 2 H, J = 7.5 Hz), 5.2 (d, 1 H, J = 9 Hz), 9.15 (d, 1 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6, 29.9, 33.1, 54.8, 94.5, 168.5, 187.0; IR (neat) 1610, 1580 cm^{-1}; HRMS; m/z 125.0825, calcd for $C_7H_{11}NO$, 125.0839.

Cyclic enaminones **5g** and **5f** were prepared by this method, and their physical properties are listed below.

5g: oil; ^1H NMR (CCl_4) δ 1.55–2.1 (m, 4 H), 2.9 (s, 3 H), 2.95 (t, 2 H, J = 7.5 Hz), 3.3 (t, 2 H, J = 7 Hz), 4.85 (d, 1 H, J = 7 Hz), 9.4 (d, 1 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 19.2, 23.1, 25.5, 40.1, 51.7, 76.9, 98.9, 164.5, 185.8; IR (neat) 1600, 1560 cm^{-1}; HRMS, m/z 139.1007, calcd for $C_8H_{13}NO$ 139.0993.

5h: oil; ^1H NMR (CCl_4) δ 1.4–1.85 (m, 6 H), 2.8–3.1 (m, 2 H), 2.95 (s, 3 H), 3.35–3.6 (m, 2 H), 4.75 (d, 1 H, J = 7 Hz), 9.35 (d, 1 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 26.0, 27.3, 27.4, 28.8, 41.0, 54.8, 101.0, 169.8, 186.8; IR (neat) 1605, 1560 cm^{-1}; HRMS, m/z 153.1150, calcd for $C_9H_{15}NO$ 153.1152.

Acknowledgment. Financial support from the Ministry of Education, Science and Culture of Japan, is deeply acknowledged.

Registry No. **1**, 6229-00-1; **3a**, 108344-13-4; **3b**, 127-19-5; **3d**, 96642-85-2; **3e**, 108344-14-5; **3f**, 872-50-4; **3g**, 931-20-4; **3h**, 2556-73-2; **5a**, 108344-15-6; **5b**, 1190-91-6; **5d**, 108344-16-7; **5e**, 108344-17-8; **5f**, 108344-18-9; **5g**, 108344-19-0; **5h**, 108344-20-3.

Toxicants from Mangrove Plants. 3. Heritol, a Novel Ichthyotoxin from the Mangrove Plant *Heritiera littoralis*[1]

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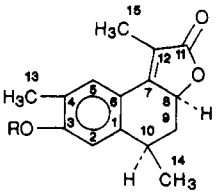
An ethnobotanical survey of mangrove vegetation in Southeast Asia revealed[2] that certain plants possess toxic

properties. Local fisherman in the Philippines reported that the sap of the mangove plant *Heritiera littoralis* is used as a fish, arrowhead, and spearhead poison. These obervations prompted this continuing chemoecological study of mangrove toxins in the Philippines. Initial studies of *H. littoralis*[3] indicated that the chloroform and ethanol extracts of the roots contained the highest level of toxicity to fish.

In this paper, we report the isolation and structure determination of the compound heritol (1) from *H. littoralis*. Heritol (1) has demonstrated ichthyotoxicity (90 min) to *Tilapia nilotica* fingerlings (25–35-mm length; 0.05–0.25-g dry weight) at a concentration of 20 ppm.

Pure heritol (1) was crystallized from methanol as white needles [mp 271–272 °C; $[\alpha]^{25}_D$ +261.3°] from a fraction obtained by chromatography (20% chloroform–benzene) on silica gel of the methylene chloride soluble portion of the chloroform soluble portion of the ethanol extract of *H. littoralis*. A molecular formula of $C_{15}H_{16}O_3$ was established by high-resolution mass spectrometry (M^+ *m/e* obsd 244.1110, calcd 244.1099). This formula indicated



1, R=H
2, R=Ac

eight degrees of unsaturation. The presence of aromaticity in the molecule was suggested by the fact that the molecular ion at *m/e* 244 was also the base peak. Furthermore, fragmentations at *m/e* 216 (M^+ – CO) and *m/e* 215 (M^+ – CHO) were typical of a phenol.

The presence of an α,β-unsaturated γ-lactone was indicated by the UV (cyclohexane) absorption at 228 nm (ϵ 11 950) and by an IR (KBr) band at 1750 cm^{-1}. A band at 3450 cm^{-1} indicated the presence of a hydroxyl group. The aromatic nature of heritol (1) was confirmed by the ^1H NMR ($CDCl_3$, 200 MHz) spectrum, which gave resonances at δ 6.85 (s, 1 H) and 7.42 (s, 1 H) for two isolated protons on an aromatic ring, and by the UV spectrum, which gave absorptions at 217, 285, and 305 nm.

A further study of the ^1H NMR spectrum provided evidence of three nonequivalent methyl resonances at δ 1.42 (d, 3 H, J = 10 Hz), 2.18 (s, 3 H), and 2.30 (s, 3 H). Two of the resonances are singlets, proof of their attachment to quaternary carbons. The third methyl group with double multiplicity can be assigned to a methine carbon. The ^1H NMR spectrum also gave signals for a methylene proton at δ 2.62 (1 H, mult), a benzylic proton at δ 3.10 (1 H, mult), a proton on a carbon bearing oxygen at δ 4.90 (dd, J = 10 and 3 Hz), and a hydroxylic proton at δ 5.22 (1 H, s). Disappearance of the resonance at δ 5.22 upon acetylation confirmed its assignment as a hydroxylic proton. Due to solubility problems with heritol in the common deuterated solvents, the decoupled ^{13}C NMR spectrum[4] was obtained in $CDCl_3$ with heritol acetate (2). The

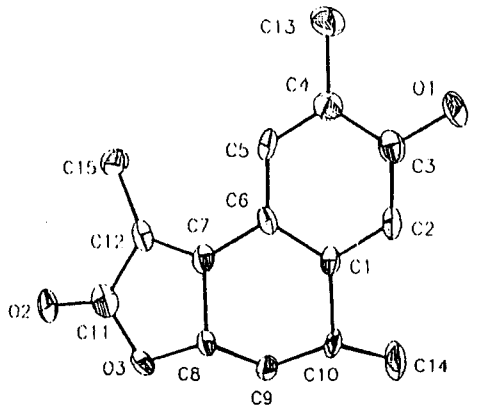
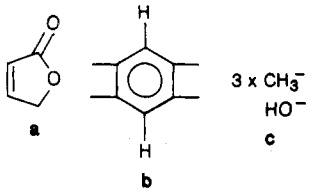


Figure 1. Computer-generated perspective drawing of heritol. Hydrogens are omitted for clarity.

spectrum gave 17 resonances, indicating a molecule with no symmetry. The resonances at 169.1 (carbonyl) and 21.4 ppm (methyl) could be attributed to the acetyl moiety. The low-intensity signal at 175.2 ppm could be assigned to the carbonyl carbon of the lactone. Six aromatic resonances were observed at 121.1, 126.5, 129.2, 130.2, 141.9, and 151.0 ppm. The intensity ratio of these lines and the presence of two lines of the same intensity at 121.1 and 130.2 ppm suggested[5] the symmetric ortho tetrasubstitution with the two protons located in the para positions. Two additional deshielded carbon resonances at 118.5 and 155.8 ppm were assigned to the α- and β-carbons of an α,β-unsaturated γ-lactone moiety. This partial skeleton was also supported by a resonance at 79.3 ppm that could be assigned to the methyl carbon that is single bonded to oxygen in the lactone functional group. The data therefore suggested that the molecule contains the following partial structures: Partial structures **a** and **b** account for seven



degrees of unsaturation, which suggested that an additional ring must be present in order to complete the unsaturation number of eight suggested by the molecule. Incorporating partial structures **a** and **b** into the ring and consideration of the isoprene rule led to the assignment of the basic skeleton of heritol (1). Further justification for this assignment was the fact that this structure contained the cadinane framework.[6,7] A single-crystal X-ray structure determination was performed to verify the structural assignment and to determine stereochemical relationships.

Figure 1 shows a computer-generated perspective drawing of the final X-ray model of heritol (1) less hydrogens. The X-ray experiment defined only the relative configuration so the enantiomer shown represents an arbitrary choice; however, this enantiomer is probably correct since it has the *R* configuration at C-10 (numbering used in this paper), which is analogous with other cadinanes.[6,7]

There is a great need for new biodegradable agrochemicals that could be compatible with the environment. Toxic compounds such as heritol (1) have potential as

(1) Part 2: Gomez, E. D. de la Cruz, A. A.; Chavez, V. B.; Miles, D. H.; Cajipe, G. J. B. *J. Philipp. Sci.* **1986**, *115*(2), 81–89.
(2) Quisumbing, E. *Medicinal Plants of the Philippines*; Manila Bureau of Printing: Philippines, 1951; p 1234.
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(4) Our tentative ^{13}C NMR assignments for the heritol skeleton of the acetylated product are 141.9 ppm (C_1), 121.1 (C_2), 151.0 (C_3), 126.5 (C_4), 130.2 (C_5), 129.2 (C_6), 155.8 (C_7), 79.3 (C_8), 31.6 (C_9), 38.6 (C_{10}), 175.2, 118.5 (C_{11}) (C_{12}), 20.8 (C_{13}), 10.0 (C_{14}), and 16.0 (C_{15}).
(5) Fieser, L. F.; Williamson, K. L. *Organic Experiments*; D. C. Heat and Co.: New York, 1983; p 435.
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natural pesticides. Plants from tropical regions of the world offer particularly intriguing possibilities in this regard since they are subjected to severe disease and insect pressures. This is especially true for mangrove plants because of their proximity to water. Heritol (1) is interesting since it possesses toxic properties and is a novel structure of the cadinane sesquiterpene class with an unusual oxygenation pattern and aromatic ring. The toxicity of heritol (1) to fish and related organisms is currently under examination for the purpose of evaluating the potential for agrochemical utilization.

Experimental Section

Isolation of Heritol (1). The dried, chopped roots of *H. littoralis* (21 kg) were extracted for 16 h in a Soxhlet extractor with *n*-hexane. The plant material was then extracted with 95% ethanol for 16 h. Evaporation of the ethanol in vacuo yielded 254 g of crude extract, which was then partitioned between chloroform and water (1:1). The chloroform solution was evaporated in vacuo to give 38.4 g of crude material. Methylene chloride was added to this material. The soluble portion (23.9 g after evaporation of the methylene chloride in vacuo) showed toxicity to fish (100% mortality in 5 h at 100 ppm) during the "quick screening test"[3] while the insoluble portion showed no activity. The methylene chloride soluble portion was chromatographed on an open column with silica gel as an absorbent. The column was eluted with hexane–benzene–chloroform–methanol solvent systems. The 20% benzene–chloroform fractions were combined. This concentrated fraction was dissolved in a minimum amount of hot methanol and heritol (1) crystallized after 24 h at room temperature in the form of white needles: mp 271–272 °C dec; $[\alpha]^{25}_D$ +261.3; IR (KBr) 3350, 3000, 1750, 1660, 1620, 1370, 1070, 890 cm^{-1}; UV (cyclohexane) λ_{max} 217 nm (ϵ 12 600), 228 (ϵ 11 950), 285 (ϵ 14 215), 305 (ϵ 8076). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.77; H, 6.65; mol wt, 244.1100. Found: C, 74.14; H, 6.81; mol wt (mass spectroscopy), 244.1110.

Other significant peaks: high-resolution mass spectrum, *m/e* (composition, %) 229 (36), 215 (19), 201 (23), 185 (20), 173 (24), 161 (17), 128 (15), 115 (13), 77 (10), 51 (7); ^1H NMR ($CDCl_3$) δ 1.42 (d, 3 H, J = 10 Hz), 2.18 (s, 3 H), 2.30 (s, 3 H), 2.62 (m, 1 H), 3.10 (m, 1 H), 4.90 (dd, J = 10 and 3 Hz), 5.22 (s, 1 H), 6.85 (s, 1 H), 7.42 (s, H).

Crystals of heritol (1) were grown by slow evaporation of methanol. Preliminary X-ray photographs revealed the orthorhombic symmetry with unit cell parameters a = 8.028 (3) Å, b = 10.286 (6) Å, c = 15.46 (9) Å, and β = 90.0°. The space group was $P2_12_12_1$ with ρ_{calcd} = 1.29 g cm^{-3} for Z = 4. Intensities were collected in the usual manner[8] with standard fluctuations of ±2%. One independent octant of data was measured to $2\theta_{max}$ = 44°, with 845 of 966 reflections considered observed ($I > 3\sigma(I)$) with no absorption correction (μ = 0.83 cm^{-1}). The structure was solved by MULTAN[9] and refined for carbon and oxygen atoms with anisotropic and thermal parameters to give R = 0.053 and R_w = 0.052. Figure 1 shows the molecular structure and numbering scheme.

Acknowledgment. This study was supported by the Divison for International Programs, National Science Foundation (INT Grant 8202732). We are indebted to Drs. Catherine Costello and Thomas Dorsey of the MIT Mass Spectrometry Facility for their invaluable assistance in obtaining the mass spectrum of heritol. We thank Dr. Jim Dechter and Vicki Farr of the University of Alabama NMR facility for their help in obtaining ^1H NMR data.

Supplementary Material Available: Listings of distances and angles, atomic positional parameters with their anisotropic thermal factors, isotropic thermal factors, and crystal data for the natural product (9 pages); observed and calculated structure factors (5 pages). Ordering information is given on any current masthead page.

(8) Holton, J.; Lappert, M. F.; Ballard, D. G.; Pearce, R.; Atwood, J. L.; Hunter, W. E. *J. Chem. Soc., Dalton Trans.* **1979**, 45.
(9) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A: Cryst. Phys., Diffr., Theor. Gen. Crystallogr.* **1971**, *27*, 368.

A Convenient Synthesis of Haloethyl Alkyl Sulfides

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The synthesis of 2-bromoethyl benzyl sulfide (**1a**) was required for the preparation of a series of compounds to be evaluated as radioprotective agents. The preparations of 2-haloethyl alkyl sulfides were reported by the routes shown in Scheme I.

Scheme I

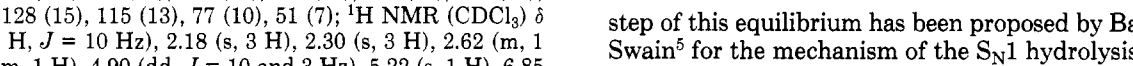
$PhCH_2SCH_2CH_2OH + HCl \rightarrow PhCH_2SCH_2CH_2Cl$ (**1b**) (ref 1)

$(EtO_2)PSCH_2Ph + Cl_2 + CH_2{=}CH_2 \rightarrow$ **1b** (ref 2)

$PhCH_2SSCH_2Ph + Cl_2 + CH_2{=}CH_2 \rightarrow$ **1b** (ref 3)

$PhCH_2SH + Br_2 + CH_2{=}CH_2 \rightarrow$ **1a** (ref 4)

We chose the last route in Scheme I[4] for the preparation of **1a**; however, from each reaction the product seemed to be contaminated with about 7% of benzyl bromide (CH_2, 4.45 ppm) as determined by proton NMR analysis of the product mixture. The formation of this impurity was not expected, and the benzyl bromide proved to be difficult to remove by distillation. One rationalization for the formation of benzyl bromide was the equilibrium formation of the cyclic sulfonium salt **2** as shown in eq 1. The first



(1)

step of this equilibrium has been proposed by Bartlett and Swain[5] for the mechanism of the S_N1 hydrolysis of β-halo sulfides such as mustard, and thus the cyclization and salt formation are not unexpected. Ogston,[6] whose studies were the basis of most of the mechanisms of reaction of mustard derivatives, conducted the displacement reaction in an aqueous solution. Thus the sulfonium salt would be expected to give primarily hydrolysis in excess water while in our reaction, the decomposition to benzyl bromide (**3**) and ethylene sulfide (**4**) was facilitated by the nonpolar solvent and the absence of any nucleophile except halide ion.

In order to test this hypothesis the synthesis of **1a** was attempted by starting with benzyl bromide (**3**) and excess ethylene sulfide. The reaction proceeded to give a quantitative yield of **1a**. A similar reaction with trityl chloride gave the novel, solid 2-chloroethyl trityl sulfide (**1c**) in 81% yield. The reaction failed with benzyl chloride. This indicates a failure of the halide to form a salt on reaction with ethylene sulfide, which is obviously a requirement for the synthesis.

$Ph_3CSCH_2CH_2Cl$
1c

The success of this synthesis to give pure samples of **1a** and **1c** is interesting in view of the problem of obtaining **1a** free of benzyl bromide when it was prepared by the ref

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