Ochtodene and Ochtodiol: Novel Polyhalogenated Cyclic Monoterpenes from the Red Seaweed *Ochtodes secundiramea*[1]

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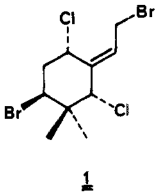
Although a diverse array of halogenated terpenoids have been isolated from marine red algae (Rhodophyta),[2] cyclic halogenated monoterpenes have been found only in the red algae *Chondrococcus hornemanni* (Mertens) Schmitz[3a,b] and several species of the genus *Plocamium.*[4a,b] From *Ochtodes secundiramea* (Montagne) Howe,[5] a Caribbean red alga which is related to *C. hornemanni* (order, Gigartinales; family, Rhizophyllidaceae), we have isolated and fully characterized two new halogenated cyclic monoterpenes. Interestingly, and contrary to *Chondrococcus* and *Plocamium* species, *O. secundiramea* does not produce substantial amounts (<0.5% of the extract) of acyclic halogenated monoterpenes.

A small collection of *O. secundiramea* was made in April 1977 near Water Key along the Belizean barrier reef. The fresh algae were stored in 2-propanol and subsequently repeatedly extracted with chloroform. Silica gel column chromatography of the combined and concentrated extracts gave first the major nonpolar component 1, next the known compound chondrocole A (2),[6] and later minor amounts of the diol 3. We suggest the trivial names ochtodene (1) and ochtodiol (3) for these new compounds.



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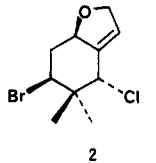

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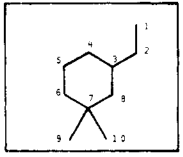

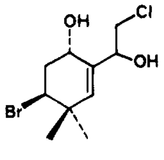

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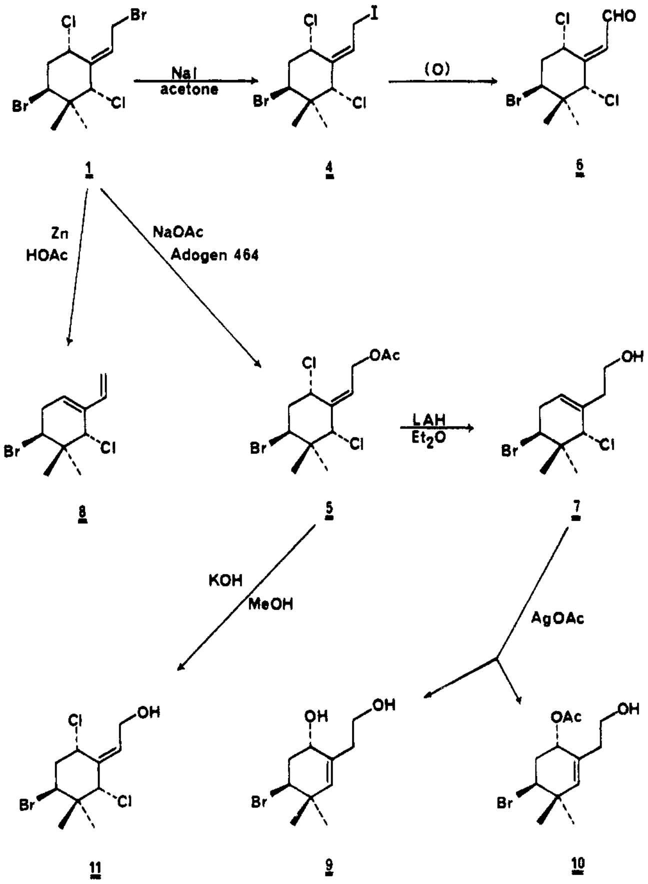
Ochtodene (1) (ca. 50% of the organic extract), mp 60–62 °C, $[\alpha]^{22}_{D}$ +179° (*c* 12, $CHCl_3$), was determined to have the molecular formula $C_{10}H_{14}Br_2Cl_2$ from the high-resolution mass measurement of the $M^+ - Br$ fragment ion and from the low intensity low-resolution mass spectral isotopic clusters for the parent ion at *m/e* 362. One of the two requisite degrees of unsaturation in this formula was accounted for by a trisubstituted olefin deduced from the ^{13}C NMR absorptions at δ 137.7 (s) and 131.9 (d). The additional degree of unsaturation was determined to be a cyclohexane ring from the remaining NMR data. The ^1H NMR spectrum of ochtodene exhibited a lone olefinic proton at δ 5.96, which was shown by spin decoupling to be coupled (J = 7 and 10 Hz) to two geminally coupled protons attached to a halogen-bearing primary carbon [δ 4.05 (1 H, J = 7 and 12.5 Hz) and 4.20 (1 H, J = 10 and 12.5 Hz)]. A gem dimethyl moiety was recognized to exist in ochtodene from the classical NMR (^1H singlets at δ 1.03 and 1.30 and ^{13}C off-resonance quartets at δ 20.4 and 28.5 and singlet at δ 41.3) and infrared (doublet absorptions at 1360 and 1380 cm^{-1}) characteristics. Three halogen-bearing secondary carbons were also observed in the ^{13}C NMR spectrum as off-resonance doublets at δ 70.0, 52.7, and 50.4. The ^1H NMR spectrum of 1 contains bands characteristic of an allylic -CHX- group (singlet at δ 4.40) and an isolated -CHX-CH_2-CHX′- constellation: δ 4.99 (1 H, dd, J = 1.8 and 4.8 Hz), 4.85 (1 H, dd, J = 4.5 and 12.5 Hz), 2.71 (1 H, ddd, J = 1.8, 4.5, and 15 Hz), 2.55 (1 H, ddd, J = 4.8, 12.5, and 15 Hz). Interpretation of the coupling constants for the latter constellation and of spin decoupling experiments led us to assign the δ 4.99 proton absorption to an equatorial α-halogen proton and the δ 4.85 band to an axial α-halogen proton.

Scheme I



The combined spectral features for ochtodene were readily interpreted to yield the gross structure as in 1. However, neither the locations and stereochemistry of the halogens nor the geometry of the double bond could be rigorously defined. Problems analogous to these have recently manifested themselves in the incorrect structure assignments of chondrocole A[3a,b] and violacene.[4b,c] Thus, it was deemed necessary to selectively degrade 1 to resolve these ambiguities.

Treatment of ochtodene with sodium iodide in acetone provided the primary iodide 4 but no 1,4-dehalogenation products. Since a simple S_N2 reaction transpired, introduction of an oxygen functionality in the primary position was conceived and the positions of the halogens were subsequently determined by the chemical transformations[7] shown in Scheme I.

The primary halogen in 1 was shown to be bromine. Treatment of ochtodene under phase-transfer conditions with sodium acetate resulted in the primary acetate 5 in high yield (96%). The spectral data of 5 clearly established the product as the primary acetate. The mass spectrum of 5 illustrated a facile loss of halogen to provide fragment ions with bromine and/or chlorine but none with three halogens or two of the same. Elemental analysis of 5, however, confirmed the presence of two chlorines and one bromine. Also, slight heating of the primary iodide 4 followed by exposure to the air resulted in a modest yield of the α,β-unsaturated aldehyde 6, which possessed a parent ion in the mass spectrum (*m/e* 298) with characteristic isotopic components for Cl_2Br.

The axial halogen which was part of the isolated -CHX-CH_2-CHX′- system in 1 was shown to be an allylic chlorine

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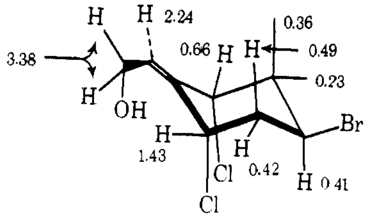
Chart I. Changes (Δδ) in Chemical Shifts of 11 after the Addition of 1 Equivalent of Eu(fod)$_3$



11

since reaction of 5 with lithium aluminum hydride in diethyl ether at 0 °C reduced not only the acetate but also displaced this chlorine to yield the cyclohexene 7. The mass spectrum of 7 revealed a $M^+ - H_2O$ fragment ion at *m/e* 248 for $C_{10}H_{14}BrCl$. The resultant endocyclic olefin proton, appearing in the ^1H NMR spectrum at δ 5.49, was shown by spin decoupling not to be coupled to the primary α-hydroxyl protons [δ 3.76 (t, J = 6.2 Hz)], thus establishing that the proposed reduction had occurred. An allylic -CHX- singlet remained (δ 4.29) for the C-8 methine, as well as a pseudoaxial halogen-bearing methine proton at δ 4.51 (dd, J = 6.1 and 10.0 Hz). The 1,4-dehalogenation product 8, resulting from reaction of 1 with zinc in acetic acid at room temperature, also showed the loss of one bromine and one chlorine by the molecular ion in the mass spectrum at *m/e* 248 ($C_{10}H_{14}BrCl$) and thus corroborated these two halogen assignments in 1. Upfield shifts of the C-6 axial proton in 7 and 8 relative to 1 reveal that the deshielding effect of one 1,3-diaxial proton–halogen interaction in the ^1H NMR spectrum is approximately 0.3 ppm.

Finally, the isolated allylic halogen in 1 was shown to be chlorine. Treatment of 7 with silver acetate in aqueous acetic acid containing tetrahydrofuran yielded the allylic alcohol 9 and allylic acetate 10 in a 4:1 ratio. The structure of the acetate 10 was confirmed by $LiAlH_4$ reduction to yield 9. Both 9 and 10 contained only one bromine atom. Interestingly, the carbonium ion which is generated from the loss of the allylic and neopentyl chlorine is trapped regio- and stereospecifically without methyl migration. In 9 and 10, the olefin proton is observed in the ^1H NMR spectrum as a singlet and the C-6 pseudoaxial methine proton remains intact as a doublet of doublets.

The geometry of the olefin in 1 was determined by an Eu(fod)$_3$-induced shift study[8] of the primary allylic alcohol 11, which was obtained by saponification of the primary acetate 5. The induced shifts of the protons in 11 indicated that the alcohol has the stereochemistry as shown in Chart I. The geometry of the olefin was clearly established as *E*, and the isolated C-8 methine proton was shown to be equatorial.[9]

Ochtodiol (3) was isolated in trace amounts (0.1% of the extract) after repeated silica gel and Florisil chromatography. Acetylation (Ac_2O/pyridine/room temperature) gave the diacetate 12, which was established to have the molecular formula $C_{14}H_{19}O_4BrCl$ by high-resolution mass measurements of the $M^+ - HOAc$ and $M^+ - HCl$ fragments. The ^1H NMR similarities between ochtodiol, its diacetate, and the two silver acetate reaction products 9 and 10 greatly facilitated the structure assignment of this diol.[9]

The C-6 halogen in 3 was assigned as a pseudoequatorial bromine based upon a comparison of the ^1H NMR band for the C-6 methine proton at δ 4.43 (dd, J = 4.8 and 11.2 Hz) with that from 8 [δ 4.44 (dd, J = 6.6 and 9.7 Hz)], and also the C-6 methine proton of 9 [δ 4.23 (dd, J = 5 and 12 Hz)] with that of 11 [δ 4.27 (dd, J = 5.8 and 11.0 Hz)]. All of these protons illustrated pseudoaxial–pseudoaxial and pseudoaxial–pseudoequatorial coupling constants. The C-6 methine proton was further determined by spin decoupling to be in an isolated $CHX-CH_2-CHY$ constellation where Y is hydroxyl. The C-4 methine proton was observed as a multiplet at δ 4.32 and was coupled to a two-proton multiplet at δ 2.30. The C-8 olefin proton appeared as a singlet at δ 5.69 and the two methyl groups as singlets at δ 1.19 and 1.07. The remaining protons at C-1 and C-2 were also related by spin decoupling and appeared at δ 4.32 (C-2 proton) and 3.62 (C-1 methylene pair). Two D_2O exhangeable protons were also observed at δ 2.95 and 3.10. They were replaced by two 3 H singlets at δ 2.07 in the spectrum of the diacetate 12. Also observable in the spectrum of the diacetate was the C-4 methine proton at δ 5.39. The coupling constants for this proton (dd, J = 2.7 and 3.6 Hz) clearly established it to be pseudoequatorial.

Ochtodes secundiramea, although relatively sparse, was one of the few collectable red algal representatives to be found in the Caribbean waters along the coast of Belize. This alga is also quite unique in its bright red-blue fluorescent appearance, which is the result of refractance from large lipid-like bodies dispersed along the cortex of the thallus of the alga. Studies of similar bodies in *Laurencia* and *Plocamium* species have shown that these bodies are the sites of storage of the products of halogen metabolism.[10] The very large concentrations of ochtodene in *O. secundiramea* (50% of the organic extract) and the sensitivity of this compound toward nucleophiles suggest that it may be stored in these refractile bodies. Indeed, when fresh plants were briefly dipped in cool ethanol, the refractile bodies were destroyed, and by TLC the ethanol extract contained ochtodene. Finally, the production of halogenated monoterpenes may result in decreased predation of this alga in an ecosystem with many rapacious herbivores. In this regard, ochtodene is physiologically active against microorganisms showing strong antibacterial activity (agar plate method, 20 mm inhibition at a 0.5 mg disc load) against *Staphylococcus aureus.*

Experimental Section

^1H NMR spectra were recorded on a Varian HR-220 spectrometer with computerized Fourier transform and spin-decoupling capabilities. ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer. Chemical shifts are expressed as δ values in ppm relative to Me_4Si = 0. Infrared spectra were obtained on a Perkin-Elmer 137 sodium chloride spectrophotometer, UV spectra were recorded on a Perkin-Elmer 124 spectrophotometer, and optical rotations were measured on a Perkin-Elmer 1410 polarimeter. Low-resolution mass spectra and high-resolution mass measurements were supplied by the Analytical Facility at the California Institute of Technology. Low-resolution GC–MS were obtained using a Hewlett-Packard 5930A mass spectrometer interfaced with a Hewlett-Packard 5910 gas chromatograph. Elemental analyses were supplied by Galbraith Laboratories, Inc., Tenn. All high pressure liquid chromatography separations were obtained using a Waters 6000 LC with 2 × 1 ft μ-porasil as the support. Melting points were measured on a Fisher-Johns apparatus and are reported uncorrected.

Collection and Extraction. *Ochtodes secundiramea* (Montagne) Howe was collected in the shallow lagoon area between the reef crest and the coral rubble on the east side of Water Key, 12 miles off the coast of Stann Creek, Belize, in April 1977.[5] The algae were stored fresh in 2-propanol. Subsequent pentane extraction of the decanted 2-propanol solution yielded 0.6 g of extract. This pentane extract was obtained to examine for highly volatile components; none were found. The algae were then homogenized and extracted with IPA/$CHCl_3$ (1:2) to yield an additional 0.47 g of extract. The total organic extract was 1.95% of the dried extracted weight of the algae.

Ochtodene (1). The crude extract (1.0 g) was applied to a silica gel column (2.5 × 45 cm) prepared with 100% petroleum ether. Ochtodene (1; 0.50 g, 0.9% of the dried extracted weight) was eluted pure with 10% diethyl ether in petroleum ether. Compound 1: mp 60–62 °C; $[\alpha]^{23}{}_D$ +179° (*c* 12.0, $CHCl_3$); high-resolution mass measurement of $M^+ -$ Br, observed *m/e* 282.969 ($C_{10}H_{14}{}^{79}Br^{35}Cl_2$ requires *m/e* 282.966); low-resolution mass spectrum (50 eV), *m/e* (halogen composition, relative intensity) 362 ($^{79}Br_2{}^{35}Cl_2$, 1.3), 327 (Br_2Cl, 7.7), 283 ($BrCl_2$, 26.0), 247 (ClBr, 18.0), 211 (Br, 23.3), 203 (Cl_2, 50.7), 167 (Cl, 100.0), 91 (86.7); ^1H NMR [$CDCl_3$ (benzene-d_6)] δ 1.03 (0.59) (3 H, s), 1.30 (1.16) (3 H, s), 2.55 (2.01) (1 H, ddd, J = 4.8, 12.5, and 15.0 Hz), 2.71 (2.40) (1 H, ddd, J = 1.8, 4.5, and 15.0 Hz), 4.05 (3.24) (1 H, dd, J =

7.0 and 12.5 Hz), 4.20 (3.48) (1 H, dd, J = 10.0 and 12.5 Hz), 4.40 (3.79) (1 H, s), 4.85 (4.85) (1 H, dd, J = 4.5 and 12.5 Hz), 4.99 (4.28) (1 H, dd, J = 1.8 and 4.8 Hz), 5.96 (5.22) (1 H, dd, J = 7.0 and 10.0 Hz); ^{13}C NMR [$CDCl_3$ (benzene-d_6)] δ 20.4 (20.2) (q), 28.5 (28.5) (q), 37.6 (37.6) (t), 41.32 (41.3) (t), 41.32 (41.6) (s), 50.41 (50.5) (d), 52.7 (53.2) (d), 69.95 (69.9) (d), 131.9 (132.0) (d), 137.7 (137.3) (s); IR (CCl_4) 2960, 2870, 1380, 1360, 897 cm^{-1}.

An epimer or double-bond isomer **1b** and a trichlorobromo analogue **1a** of ochtodene (**1**) were also detected in fractions containing mixtures from silica gel chromatography (10% diethyl ether in petroleum ether). The low-resolution GC–MS of **1a** provided the following: m/e 318 (M^+, $C_{10}H_{14}{}^{35}Cl_3{}^{79}Br$, 2.6), 283 ($Cl_2Br$, 17.8), 239 ($Cl_3$, 15.8), 203 ($Cl_2$, 79.5), 187 ($Cl_2$, 23.6), 167 (Cl, 100.0), 131 (47.9), 91 (75.3).

The low-resolution GC–MS of **1b** was quite similar to **1** in ion fragments: m/e 362 (M^+, $C_{10}H_{14}{}^{79}Br_2{}^{35}Cl_2$, 1), 327 ($Br_2Cl$, 5.6), 283 ($BrCl_2$, 37.3), 247 (BrCl, 20.9), 211 (Br, 20.2), 203 (Cl_2, 39.6), 167 (Cl, 94.0), 91 (100.0).

Retention times using temperature programming (160–250 °C, 2-min delay, 16 °C/min) on a 2 M 3% SP-2401 column (He flow, 60 mL/min) were 5.0 min for **1**, 4.1 min for **1b**, and 3.45 min for **1a**.

Chondrocole A (2). Elution of pure chondrocole A (**2**) (0.04 g) was facilitated by silica gel chromatography using 25% diethyl ether in petroleum ether. The NMR and mass spectra and optical rotation of **2** were identical with those of an authentic sample of chondrocole A obtained from the red alga *Chondrococcus hornemanni* (Mertens) Schmitz collected in Hawaii.[6]

Aldehyde 6. Sodium iodide (0.05 g, 0.33 mmol) was added with stirring to an ice-cooled solution of **1** (0.06 g, 0.165 mmol) in 15 mL of acetone. After 5 min, the ice bath was removed and the solution was stirred for an additional 15 min. To the acetone solution was added 15 mL of saturated NaCl solution, and the aqueous phase was extracted with 3 × 35 mL of diethyl ether. The combined organic phases were washed twice with 15 mL of saturated NaCl solution, dried ($MgSO_4$), and reduced in volume in vacuo to yield 60 mg of an oily residue. ^{1}H NMR (benzene-d_6) revealed a 1:2 mixture of **1** and the primary allylic iodide (**4**): δ 0.61 (3 H, s), 1.16 (3 H, s), 2.09 (1 H, ddd, J = 5, 12.5, and 15.0 Hz), 2.41 (1 H, ddd, J = 1.8, 4.5, and 15.0 Hz), 2.95 (1 H, dd, J = 7.5 and 10.0 Hz), 3.25 (1 H, dd, J = 10.0 and 10.5 Hz), 3.79 (1 H, s), 4.38 (1 H, dd, J = 1.8 and 5.0 Hz), 4.86 (1 H, dd, J = 4.5 and 12.5 Hz), 5.23 (1 H, dd, J = 7.5 and 10.5 Hz)

Simply removing the benzene-d_6 under vacuum followed by exposure to air caused extensive decomposition. From this dark violet oily material, the aldehyde **6** was obtained (10 mg) by repeated LC purification using 25% diethyl ether in hexane as the solvent system. Compound **6**: ^{1}H NMR ($CDCl_3$) δ 1.02 (3 H, s), 1.30 (3 H, s), 2.50 (1 H, ddd, J = 4, 10, and 15 Hz), 2.71 (1 H, ddd, J = 2, 5, and 15 Hz), 4.33 (1 H, s), 4.77 (1 H, dd, J = 5 and 10 Hz), 5.51 (1 H, dd, J = 2 and 4 Hz), 6.01 (1 H, d, J = 7 Hz), 9.94 (1 H, d, J = 7 Hz); IR ($CHCl_3$) ($\nu_{C=O}$) 1683 cm^{-1}; low-resolution mass spectrum (50 eV), m/e 298 (M^+, $BrCl_2$, 0.3), 283 ($BrCl_2$, 1.4), 263 (BrCl, 2.5), 247 (BrCl, 2.1), 227 (Br, 9.3), 183 (Cl, 10.0).

Acetate 5. Ochtodene (**1**; 0.0159 g, 0.044 mmol) was added to 2 mL of CCl_4 and 1 mL of H_2O. $NaOAc{\cdot}3H_2O$ (0.009 g, 0.066 mmol) was then added with stirring. After the sodium acetate had dissolved, 1 drop of Adogen 464 (Aldrich Chemical Co.) was added. The mixture was refluxed for 3 h. Saturated NaCl solution (10 mL) was added, and the aqueous phase was extracted with 3 × 30 mL of diethyl ether. The combined ether layers were then dried ($MgSO_4$) and reduced in vacuo. Purification by LC using 10% diethyl ether in hexane provided 16.3 mg (96%) of the acetate **5**: ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, s), 1.30 (3 H, s), 2.09 (3 H, s), 2.55 (1 H, ddd, J = 5, 13, and 14 Hz), 2.70 (1 H, ddd, J = 2, 5, and 14 Hz), 4.39 (1 H, s), 4.56 (1 H, dd, J = 5 and 14 Hz), 4.83 (1 H, dd, J = 5 and 13 Hz), 5.07 (1 H, dd, J = 2 and 5 Hz), 5.84 (1 H, dd, J = 5 and 8 Hz); IR (CCl_4) ($\nu_{C=O}$) 1725 cm^{-1}; low-resolution mass spectrum (50 eV), m/e 307 (BrCl, 31.3), 271 (Br, 4.7), 247 (BrCl, 21.9), 229 (Br, 25.0), 167 (Cl, 50.0). Elemental analysis: 19.71% Br (calcd, 26.5%).

$LiAlH_4$ Reduction. Cyclohexenol 7. Excess $LiAlH_4$ (ca. 6 mg) was added to a well-stirred and ice-cooled solution of **5** (0.021 g, 0.0544 mmol) in 10 mL of anhydrous diethyl ether under argon. The mixture was stirred for 0.5 h at 0 °C and then quenched by adding H_2O dropwise until no further reaction occurred. A pinch of $MgSO_4$ was added with stirring. The reaction mixture was then filtered, and the filtrate was washed with 30 mL of diethyl ether. After reducing the ether solution under vacuum, the residue was chromatographed by preparative silica gel thin-layer chromatography (diethyl ether/benzene (1:1), 0.2 mm sheets; R_f 0.32–0.50) to yield 9 mg of pure alcohol **7**: ^{1}H NMR ($CDCl_3$) δ 1.11 (3 H, s), 1.27 (3 H, s), 2.39 (2 H, mult), 2.64 (1 H, mult), 2.85 (1 H, mult), 3.76 (2 H, t, J = 6.2 Hz), 4.29 (1 H, s), 4.51 (1 H, dd, J = 6.1 and 10.0 Hz), 5.49 (1 H, mult); IR (CCl_4) (ν_{OH}) 3600 cm^{-1}; low-resolution mass spectrum (50 eV), m/e 248 (BrCl, 20.0), 213 (Br, 16.7), 169 (Cl, 40.0), 133 (80.0), 91 (100.0).

Diene 8. Zinc dust (0.025 g, 0.385 mmol) was added with stirring to **1** (0.025 g, 0.069 mmol) in 2 mL of dry acetic acid at room temperature. After stirring for 1 h, 10 mL of diethyl ether was added, the mixture was filtered, and the filtrate was washed with ether. The solvent was then removed in vacuo. After repeated purification by LC using 5% diethyl ether in hexane and then 100% 2,2,5-trimethylpentane, 5 mg of the diene **8** was isolated: ^{1}H NMR ($CDCl_3$) δ 1.08 (3 H, s), 1.33 (3 H, s), 2.73 (1 H, mult), 2.93 (1 H, mult), 4.51 (1 H, s), 4.59 (1 H, dd, J = 6.1 and 12.0 Hz), 5.14 (1 H, d, J = 11.2 Hz), 5.33 (1 H, d, J = 17.5 Hz), 5.65 (1 H, dd, J = 2 and 7 Hz), 6.24 (1 H, dd, J = 11.2 and 17.5 Hz); UV λ_{max} (MeOH) 232–233 nm (ϵ 15 400); low-resolution mass spectrum (75 eV), m/e 248 (M^+, BrCl, 16.7), 213 (Br, 7.7), 169 (Cl, 96.7), 130 (100.0), 91 (43.3).

Silver Acetate Reaction. Cyclohexenediol 9 and Cyclohexenol Acetate 10. Compound **7** (0.011 g, 0.042 mmol) was dissolved in 2 mL of tetrahydrofuran, 1 mL of acetic acid, and 1 mL of water. Silver acetate (0.010 g, 0.060 mmol) was added with stirring, and the mixture was refluxed for 2 h. Brine (15 mL) was added, and the aqueous phase was extracted with 3 × 25 mL of diethyl ether. The combined ether layers were washed with 4 × 10 mL of saturated $NaHCO_3$, 10 mL of 5% HCl, and 2 × 10 mL of brine, dried ($MgSO_4$), and reduced in vacuo. The diol (4 mg) was isolated by silica gel column chromatography (1 × 30 cm) by elution with 100% diethyl ether. Compound **9**: ^{1}H NMR ($CDCl_3$) δ 1.08 (3 H, s), 1.24 (3 H, s), 2.23–2.32 (4 H, m), 3.65 (1 H, ddd, J = 4, 9, and 10 Hz), 3.65 (1 H, brd s; D_2O exchangeable), 3.87 (1 H, ddd, J = 5, 9, and 10 Hz), 4.05 (1 H, dd, J = 3 and 5 Hz), 4.44 (1 H, dd, J = 6.6 and 9.7 Hz), 5.45 (1 H, s); low-resolution mass spectrum (75 eV), m/e 248 (M^+, Br, 5.6), 217 (Br, 8.9), 169 (40.7).

The acetate **10** (1 mg) was also isolated by column chromatography: ^{1}H NMR ($CDCl_3$) δ 1.07 (3 H, s), 1.25 (3 H, s), 2.07 (3 H, s), 2.20 (2 H, mult), 2.34 (2 H, mult), 3.66 (2 H, t, J = 5 Hz), 4.23 (1 H, dd, J = 5 and 12 Hz), 5.23 (1 H, dd, J = 3 and 6 Hz), 5.57 (1 H, s). The structure of the acetate **10** was confirmed by $LiAlH_4$ reduction to provide material identical (NMR and mass spectra) with the diol **9**.

Allylic Alcohol 11. A 5% solution of KOH (0.4 mL) in anhydrous methanol was added with stirring to an ice-cooled solution of the acetate **5** (0.019 g, 0.049 mmol) in 5 mL of MeOH. Stirring was continued for 5 h at 0 °C. A 5% HCl solution (aqueous, 1 mL) was then added, the excess methanol was removed under vacuum, and the residue was taken up in 50 mL of diethyl ether. The organic solution was washed twice with 2 × 10 mL of saturated NaCl solution, dried ($MgSO_4$), and reduced in vacuo. Preparative silica gel thick-layer chromatography (diethyl ether/benzene (1:1), 1.5 mm plates; R_f 0.2–0.4) yielded 10 mg of the alcohol **11**: ^{1}H NMR ($CDCl_3$) δ 1.02 (3 H, s), 1.31 (3 H, s), 2.52 (1 H, ddd, J = 5, 12, and 15 Hz), 2.68 (1 H, ddd, J = 2, 5, and 15 Hz), 4.35 (2 H, d, J = 6 Hz), 4.42 (1 H, s), 4.86 (1 H, dd, J = 5 and 15 Hz), 5.00 (1 H, d, J = 2 and 5 Hz), 5.93 (1 H, t, J = 6 Hz); IR ($CDCl_4$) (ν_{O-H}) 3500 cm^{-1}; low-resolution mass spectrum (50 eV), m/e 265 (BrCl, 12.9), 229 (BrCl, 4.8), 203 (Br, 11.3).

Lanthanide Shift Study of 11. Aliquots of $Eu(fod)_3$ in $CDCl_3$ were added to compound **11** in $CDCl_3$, and the 220 MHz ^{1}H NMR spectrum was recorded. A plot of chemical shift (δ) vs. $[Eu(fod)_3]/[\mathbf{11}]$ was constructed, and a least-squares fit of the slopes normalized to 1 molar equiv of shift reagent was obtained for each absorption using the following formula: slope ($\Delta\delta$) = $[n(\Sigma xy) - (\Sigma x)(\Sigma y)]/[n(\Sigma x^2) - (\Sigma x)^2]$, where $x = [Eu(fod)_3]/[\mathbf{11}]$ and y = chemical shift (δ).[8] Assuming that the principal magnetic axis of $Eu(fod)_3$ was collinear with the europium–oxygen bond in solution, the simplified form of the general dipolar (pseudocontact) contribution equation, $\Delta\delta = \kappa(3\cos^2\theta - 1)/r^3$, was used for calculations. Distances and angles were measured using a Dreiding model of **11** after fixing the europium–oxygen bond distance at 2.7 Å and the carbon–oxygen–europium bond angle at ca. 120°. The methyl protons were treated as a single proton with a bond length of 1.94 Å from the quaternary ring carbon. Positioning the europium atom such that the resultant constants κ for each respective proton deviated minimally provided the data in Table I.

Ochtodiol (3) and the Diacetate 12. Ochtodiol (**3**) was eluted as a mixture during silica gel chromatography with 100% diethyl ether. It was separated from pigments by elution from a Florisil column on chromatography (0.5 × 10 cm) with 100% diethyl ether. **3** (5 mg) was finally obtained pure after two successive silica gel column chromatographies using increasing percentages of diethyl ether in petroleum ether: 220 MHz ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 3 H), 1.19 (s, 3 H), 2.28–2.32 (2 H, m), 2.95 (1 H, brd s; D_2O exchangeable), 3.1 (1 H, brd s; D_2O exchangeable), 3.62 (2 H, m), 4.32 (2 H, m), 4.43 (1 H, dd, J = 4.8 and 11.2 Hz), 5.69 (s).

Acetylation of **3** was effected by treatment with excess pyridine and acetic anhydride at room temperature for 2 h and removal of the ex-

Table I

δ	$\Delta\delta$	r_{measd}, Å	θ	r_{calcd}, Å	% r
4.35	3.376				
5.93	2.236	4.4	36	4.20	4.5
5.00	1.429	5.8	23	5.71	1.6
4.42	0.663	6.7	35	6.51	2.8
2.52	0.497	7.8	28	7.74	0.8
4.86	0.415	8.7	18	8.92	2.5
2.68	0.442	8.4	21	8.70	3.4
1.02	0.363	8.0	34	7.96	0.5
1.30	0.227	9.6	31	9.70	1.0

cess reagent in vacuo to yield 6 mg of the diacetate **12:** $[\alpha]^{23}{}_{\text{D}}$ −37.0° (*c* 0.33, $CHCl_3$); high-resolution mass measurement of $M^+ - HCl$ (obsd, *m/e* 330.044; calcd, *m/e* 330.047) and $M^+ -$ HOAC (obsd, *m/e* 307.014; calcd, *m/e* 307.010); ^{1}H NMR ($CDCl_3$) δ 1.07 (3 H, s), 1.18 (3 H, s), 2.07 (6 H, s), 2.35 (2 H, m), 3.64 (2 H, m), 4.27 (1 H, dd, J = 5.8 and 11.0 Hz), 5.31 (1 H, dd, J = 5.8 and 7.2 Hz), 5.39 (1 H, dd, J = 2.7 and 3.6 Hz), 5.91 (1 H, s).

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Registry No.—**1**, 67237-02-9; **3**, 67237-01-8; **4**, 67237-03-0; **5**, 67237-04-1; **6**, 67237-05-2; **7**, 67237-06-3; **8**, 67237-07-4; **9**, 67237-08-5; **10**, 67237-09-6; **11**, 67237-10-9; **12**, 67237-11-0.

References and Notes

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(5) We wish to thank Dr. James Norris, Smithsonian Institution, for aid in the collection and identification of *O. secundiramea.* A voucher specimen has been deposited in the U.S. National Herbarium, Washington, D.C.
(6) We gratefully acknowledge F. X. Woolard and R. E. Moore for providing new structural information and a sample of authentic chondrocole A.[3a] The depiction of **2** with the halogens transposed relative to the published structure is due to a recent revision of structure based upon X-ray studies.
(7) The trisubstituted olefin in ochtodene could not be oxidatively cleaved under a variety of conditions: (a) O_3/CH_2Cl_2 or EtOAc, −78 °C to room temperature; (b) $KMnO_4$, 18-crown-6, benzene, room temperature, 20 h; (c) $RuO_2/NaIO_4$, CH_2Cl_2/H_2O, room temperature, 12 h; (d) $KMnO_4$, $MgSO_4$, H_2O/acetone, −78 °C to room temperature, 1 h.
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α,α-Dichlorocyclopropanols. Attenuation of Cyclopropyl Rearrangement Processes in the 3-Bicyclo[4.1.0]heptene System. A Novel Regiospecific 2-Chlorotropone Synthesis

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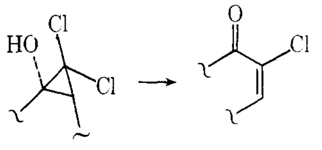
α,α-Dichlorocyclopropanols **1** rearrange with facility to α-chloroenones **2**, illustrating a transformation that has been synthetically employed in one-carbon ring expanding[1-3] or chain homologating[3,4] sequences. Indeed, these compounds are believed to thermally rearrange rapidly upon their in situ generation. However, we have recently uncovered a class of bicyclic, tertiary α,α-dichlorocyclopropanols which possess unusual thermal stability.[1,6b] The stable α,α-dichlorocyclopropanols were incorporated in the norcar-3-en-1-ol structure **3** and suggested an investigation of dichlorocyclopropanol stability with respect to olefin regioposition in the norcarene bicyclic system. We now report the results of these studies. In addition, we describe some chemistry of the compounds encountered in these studies, including a regiospecific cyclohexenone to α-chlorotropone conversion.



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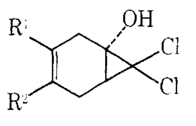

3

The three isomeric 7,7-dichloronorcaren-1-ol compounds desired for our studies have structures **4a, 5a,** and **6a.** Facile entry into these materials was provided by sodium trichloroacetate mediated and regiospecific dichlorocyclopropanation of the corresponding dienol silyl ethers **4c, 5c,** and **6c.**[1,5] In this fashion, we have prepared the silyl ethers corresponding to the desired norcarenol olefin isomers **4b** and **5b** and to an alkylated derivative **7b.** In addition, the saturated parent trimethylsilyl 7,7-dichloronorcaran-1-yl ether **8b,** previously synthesized by Conia et al. as the dibromo derivative (Cl = Br),[3] was prepared. Methanolic acid-catalyzed hydrolysis of the trialkylsilyl ether is thought to release the desired dichlorocyclopropanol structures **4a, 5a, 7a,** and **8a.** Under these reaction conditions (vide infra), only dichloronorcarenol **4a** possesses stability. The products **9** and **10** (from **5b**) and **11** (from **7b**) of the isomeric silyl norcarenyl ether compounds **5b** and **7b** are exclusively ring-expanded α-chlorocycloheptenones, which arise by way of the intermediate α,α-dichlorocyclopropanols **5a** and **7a** via rearrangement. Such a sequence has been implied for the trimethylsilyl 7,7-norcaran-1-yl ether **8b** (Cl = Br) to 2-bromocycloheptenone **12** (Cl = Br) conversion.[3]

Our studies could not detect chemical intermediates in the silyl ether hydrolysis–hydroxy cyclopropyl ring expansion transformation of compounds **5b, 7b,** or **8b** (TLC) [room temperature, pH adjusted methanolic aqueous hydrochloric acid]. In these instances, formation of α-chloroenone products appeared coincident with norcarenyl silyl ether hydrolysis. In contrast, the isolated α,α-dichlorocyclopropanol 4a was stable (85% recovery, no detectable UV absorption by TLC) to refluxing acidic aqueous 2-propanol for 20 h and could be purified via Kugelrohr distillation at 145 °C (0.1 mm). Two studies on alternate catalytic methodology to facilitate the rearrangement of **4a** deserve mention. Mildly basic treatment of cyclopropanol **4a** [methanolic $NaHCO_3$ or $Ba(OH)_2$] or base assisted hydrolysis of silyl ethers **5b, 7b,** or **8b** generated carboxylic acid compounds directly (no detectable intermediates), presumably via the corresponding α-chlorodienone, which is rapidly consumed in a Favorski ring contraction sequence. Attempted catalysis of chloride ionization with monovalent silver ion had little effect on **4a** with moderate substrate to Ag^+ ratios (3.0 equiv of $AgClO_4$ in refluxing methanol, 12 h) and converted **4a** directly to tropone with high ratios (1:15), albeit in low yield (~20%).[6]

The stability afforded the α,α-dichlorocyclopropanol function in **4a** by the appositely positioned carbon–carbon unsaturation is dramatic. However, stabilization of the cyclopropane moiety embraced in the Δ^3-norcarene system is not unique. In fact, such stabilization appears to be generally

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