Anal. Calcd for $C_{21}H_{17}BrN_4O_4$: C, 53.75; H, 3.65; N, 11.94. Found: C, 53.55; H, 3.68; N, 11.85.

2-(2-Bromophenyl)-3-phenyl-1-propanol (7a). Crude 2-(2-bromophenyl)-3-phenylpropanal (3.83 g, 13.2 mmol) was dissolved in 50 mL of 2-propanol and stirred while 500 mg (13.2 mmol) of sodium borohydride was added all at once. Stirring was continued for an additional 21 h at 25 °C. The reaction mixture was quenched by the dropwise addition of acetic acid (ca. 10 mL) and then was concentrated (rotary evaporator). Ether (50 mL) and water (100 mL) were added to the residue, and the water layer was extracted repeatedly with ether (3 × 50 mL). The combined organic solution was washed with sodium bicarbonate solution and saturated sodium chloride solution and finally was dried and concentrated to 3.82 g (99%) of pale yellow oil. This material gave a single peak on VPC analysis: ^{1}H NMR ($CDCl_3$) δ 1.79 (br s, 1, OH, exchangeable with D_2O), 2.80–3.16 (m, 2, $ArCH_2$), 3.73 (br s, 3, CH_2OH and Ar H), 6.80–7.40 (m, 8, Ar H), 7.40–7.68 (br d, 1, *o*-BrAr H); IR (neat) 3375 (OH).[24] The analytical sample was prepared by distillation; bp 140.5–143.5 (0.09 torr).

Anal. Calcd for $C_{15}H_{15}BrO$: C, 61.87; H, 5.19; Br, 27.44. Found: C, 61.68; H, 5.27; Br, 27.38.

2-(2-Bromophenyl)-1-hexanol (7b). The butylated nitrile **6b** (14.0 g, 55.52 mmol) was subjected to reduction by DIBAL (66.62 mmol) in 200 mL of toluene and worked up as in the reduction of **6a**. The product was a yellow oil (13.8 g, 54.08 mmol) which showed but a single peak on VPC analysis: ^{1}H NMR ($CDCl_3$) δ 0.60–2.48 (m, 9, $CH_2CH_2CH_2CH_3$), 4.14 (unsym t, 1, CHCHO, 6.96–7.82 (m, 4, Ar H), 9.70 (s, 1, CHO); IR (neat) 1738 cm^{-1} (C=O). This material was used without purification in the sodium borohydride reduction. The yellow oil (14.17 g, 15.52 mmol) was dissolved in 50 mL of 2-propanol and reduced with sodium borohydride as in the preparation of **7a**. The crude alcohol (**7b**, 13.37 g) was subjected to distillation in a short-path apparatus, affording 8.34 g (58% from **6b**) of a colorless oil: bp 93–99 °C (0.04 torr); ^{1}H NMR ($CDCl_3$) δ 0.60–2.20 (m, 9, $CH_2CH_2CH_2CH_3$), 1.92 (br s, 1, OH), 3.29–3.6 (m, 1, $CHCH_2OH$), 3.6–4.0 (m, 2, $CHCH_2OH$), 6.98–7.90 (m, 4, Ar H); IR (neat) 3340 cm^{-1} (OH).

Anal. Calcd for $C_{12}H_{17}BrO$: C, 56.04; H, 6.66. Found: C, 55.67; H, 6.60.

1-Benzylbenzocyclobutene (4, R = $PhCH_2$). The triphenylphosphine–bromine complex[18b] was prepared from 3.45 g (13.15 mmol) of triphenylphosphine in 60 mL of dry acetonitrile, and 3.82 g (13.12 mmol) of alcohol **7a** in 25 mL of acetonitrile was added over 5 min. The resulting pale yellow solution was stirred for 4 h at 25 °C and then was concentrated with a rotary evaporator having Teflon seals. The resulting orange syrup was vacuum distilled via short path to afford the bromide as 2.96 g (64%) of a colorless oil: bp 146.5–152.5 °C (0.08 torr); ^{1}H NMR ($CDCl_3$) δ 2.92–3.21 (m, 2, CH_2Ar), 3.48–3.7 (m, 2, CH_2Br), 3.7–4.13 (m, 1, $ArCHCH_2Br$), 6.88–7.92 (m, 9, Ar H), IR (neat) 1601 cm^{-1} (C=C).[19] To the colorless oil (5.66 g, 16.0 mmol) in 200 mL of tetrahydrofuran and 50 mL of hexane stirred and cooled to −100 °C was added 16.0 mmol of butyllithium at such a rate that the temperature did not exceed −95 °C. After 30 min at −100 °C the mixture was warmed to −78 °C and maintained at that temperature for 2 h. It was then allowed to warm to 25 °C and to remain at that temperature overnight. The reaction mixture was poured into 100 mL of water, the layers were separated, and the aqueous layer was extracted with ether (3 × 75 mL). The combined organic layers were washed with saturated sodium chloride solution, dried, and concentrated to afford 3.57 g of a pale yellow oil. The oil which by VPC appeared to be >90% homogeneous was subjected to chromatography on silica gel (200 g) with CH_2Cl_2–petroleum ether as the eluant and afforded 2.42 g (78%) of 1-benzylbenzocyclobutene as a colorless oil: ^{1}H NMR δ 2.67–3.58 (m, 4, $ArCH_2$), 3.58–3.99 (m, 1, methine proton), 6.57–7.83 (m, 9, Ar H); ^{13}C NMR ($CDCl_3$) δ 36.20, 40.56, 44.47, 122.33, 123.24, 126.33, 126.69, 127.54, 128.52, 128.97, 141.08, 143.75, 149.35.

Anal. Calcd for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.61; H, 7.47.

1-Bromo-2-(2-bromophenyl)hexane (8b). To 31.11 mmol of triphenylphosphine–bromine complex[18b] was added 8.0 g (31.11 mmol) of alcohol **7b**, and the mixture was allowed to react as in the reaction of **7a**. After the usual workup involving concentration under reduced pressure, the residue was purified by two distillations under reduced pressure, affording 6.36 (64%) of a colorless oil: bp 92.5–95.0 °C 0.13 torr); ^{1}H NMR ($CDCl_3$) δ 0.60–2.50 (m, 9, Bu), 3.36–4.20 (m, 3, $ArCHCH_2Br$), 7.05–8.03 (m, 4, Ar H).

Anal. Calcd for $C_{13}H_{16}Br_2$: C, 45.03; H, 5.04; Br, 49.93. Found: C, 45.18; H, 5.07; Br, 49.94.

1-Butylbenzocyclobutene (4, R = Bu). The dibromide **8b** (2.5 g, 6.04 mmol) was subjected to halogen–metal exchange with butyllithium at −100 °C, cyclized essentially as described in the preparation of **4** (R = $PhCH_2$), and worked up in the usual way. The crude oil remaining after vacuum evaporation of the solvents was purified by column chromatography on silica gel with hexane as eluant, affording 2.07 g (86%) of 1-butylbenzocyclobutene as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.63–1.98 (m, 9, Bu), 2.32–3.61 (m, 5, benzylic H), 6.83–7.31 (m, 4, Ar H); ^{13}C NMR ($CDCl_3$) δ 14.13, 22.85, 30.60, 34.24, 36.20, 43.62, 122.07, 123.18, 126.75, 127.21, 144.14, 150.32.

Anal. Calcd for $C_{12}H_{16}$: C, 89.93; H, 10.06. Found: C, 89.89; H, 10.29.

Registry No. **4** (R = Bu), 78920-29-3; **4** (R = $PhCH_2$), 78920-30-6; **5**, 19472-74-3; **6a**, 78920-31-7; **6b**, 58830-40-3; **6c**, 78920-32-8; **7a**, 78920-33-9; **7b**, 78920-34-0; **8a**, 78939-71-6; **8b**, 78920-35-1; benzyl bromide, 100-39-0; butyl bromide, 109-65-9; 5-bromo-1-pentene, 1119-51-3; 2-(2-bromophenyl)-3-phenylpropanal, 78920-36-2; 2-(2-bromophenyl)-3-phenylpropanal DNP, 78920-37-3.

(24) There was no significant absorption at 1728 cm^{-1} (C=O) and in the ^{1}H NMR spectrum no evidence of the aldehyde proton at 9.71 ppm.

Sesquiterpene Lactones of *Eremanthus incanus* and *Porella japonica*. Crystal Structure and Stereochemistry of Eregoyazidin

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Eremanthus species (Compositae, Vernoniae) are rich sources of guaianolides which possess schistosomicidal properties.[1] In previous paper,[1,2] one of us reported isolation of schistosomicidal and cytotoxic heliangolides and eremanthanolides together with eregoyazin (1) and eregoyazidin (2) from *Eremanthus incanus* and *E. goyazensis*. The crystal structure and stereochemistry of eregoyazin (1) has recently been established by X-ray crystallographic analysis.[1] For eregoyazidin, and 11,13-dihydroderivative, structure **2** with C(4) and *C(11)*-methyl groups α was proposed on the basis of ^{13}C NMR and CD spectral data.[1,2] However, the stereochemistry at C(4) remained somewhat uncertain because of the seemingly enantiomeric nature of the CD curves of eregoyazin and eregoyazidin in the ketone n,π* region.[2]

Some liverworts belonging to the Jungermanniales and the Marchantiales elaborate strongly allergenic and cytotoxic sesquiterpene lactones.[3-12] In particular, a leafy

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Chart I

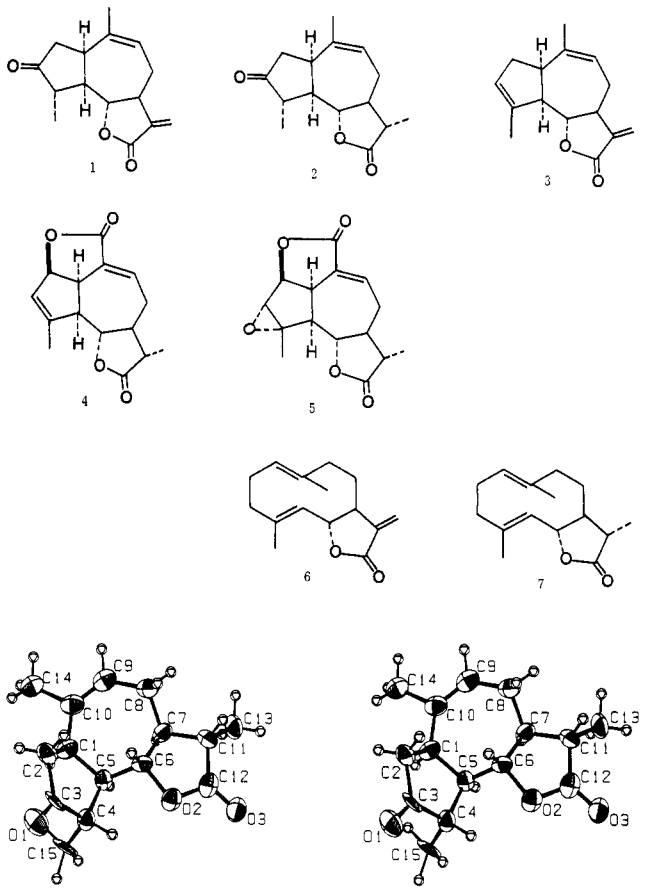

Figure 1. Stereoscopic view of eregoyazidin (2).

liverwort, *Porella japonica* Lac. (Mitt.), produces various guaianolides with plant growth inhibitory activity. Recently, some of us isolated eregoyazidin, isoeremanthin (3), porelladiolide (4) and 3,4-α-epoxyporelladiolide (5) and two related germacranolides (6, 7) from this species. As eregoyazidin was obtained in respectable yield and formed suitable crystals, we reinvestigated its stereochemistry by X-ray crystallography. This showed that eregoyazidin was 2 as previously deduced on the basis of spectral data.

Figure 1 is an ORTEP stereoview of the molecule, which shows that the methyl groups attached to C(4) and C(11) are α. Because of the correlation with eregoyazin, the figure also represents the absolute configuration. The structural parameters, except for those of the lactone ring, closely resemble those of eregoyazin (1).[1] In the eregoyazidin molecule, the conformation of the lactone ring is a half-chair as is that of the cyclopentane ring. The cycloheptane ring, in which carbon atoms C(8), C(9), C(10), and C(11) are coplanar to within 0.03 Å, adopts a distorted chair form. The C(8)–C(9)–C(10) angle of 132.4 (6)°, the C(9)–C(10)–C(1) angle of 130.2 (6)°, and the C(10)–C(1)–C(5) angle of 122.9 (5)° are unusually large, probably for reasons of ring strain. Tables I–V listing final atomic parameters for nonhydrogen atoms, coordinate parameters for hydrogen atoms, bond lengths, bond angles and selected torsion angles are available as supplementary material.

The stereochemistry proposed for the two new guaiane-type dilactones porelladiolide (4) and 3,4-α-epoxyporelladiolide (5) was based on extensive NMR studies, the remaining ambiguity being the configuration of the C(11) methyl group.[10] Because of the co-occurrence of eregoyazidin (2), (+)-costunolide (6), and (+)-dihydrocostunolide (7), the latter two of which may be the precursors of guaianolides (1–5), and because of the striking similarity between the ^{13}C NMR spectra of the α-methyl-γ-butyrolactone moieties of eregoyazidin (2) on the one hand and the porelladiolides (4, 5) on the other,[10] we are further inclined to the belief that the two new liquid dilactones have formulas 4 and 5, which embody a stable quasi-equatorial C(11) methyl group.

From the phytochemical point of view it is noteworthy that spore-forming plants such as *Porella japonica* and some other liverworts[3-12] produce the same guaianolides, germacranolides, and eudesmanolides in large quantity as are found in Compositae.

Experimental Section

Extraction and Isolation of Eregoyazidin (2).[10] *Porella japonica* Lac. (Mitt.) collected in Kito, Nakagun, Tokushima, Japan, in Sept 1980 was air-dried and ground. The ground material (670 g) was extracted with ether for 15 days. The crude green oil (19.65 g) was directly chromatographed on silica gel by using an *n*-hexane–EtOAc gradient. The fraction eluted with 1:1 *n*-hexane–EtOAc (1.30 g) was rechromatographed on silica gel with a $CHCl_3$–MeOH gradient to afford the crude sesquiterpene lactones which were purified by preparative TLC to afford eregoyazidin (2, 130 mg) whose spectral data were identical with those of eregoyazidin isolated from *Eremanthus incanus*.[2]

X-ray Analysis of Eregoyazidin (2). Crystals of eregoyazidin (2) were obtained by slow evaporation from aqueous ethanol solution. They were orthorhombic, space group $P2_12_12_1$, with a = 12.517 (2) Å, b = 15.621 (3) Å, c = 6.799 (1) Å, and D_{calcd} = 1.240 g cm^{-3} for Z = 4. The intensities were measured on a Rigaku automatic four-circle diffractometer with Mo Kα radiation by θ–2θ scans. A total of 1043 reflections were measured for $2\theta < 45°$, of which 980 were considered to be observed [$I > \sigma(I)$]. Data were corrected for Lorentz, polarization, and background effects but not for absorption. The structure was solved by the direct method using the program MULTAN[13] and refined by block-diagonal least-squares methods with anisotropic temperature factors. The atomic scattering factors used were those found in the literature,[14] except for the hydrogen scattering factor which is taken from Stewart, Davidson, and Simpson.[15] All of the hydrogen atoms were located in a difference Fourier map. The hydrogen atom contributions were included in subsequent structure factor calculations (B = 3.0 Å^2), but their parameters were not refined. The final R value reduced to 0.0571 (R_w = 0.0569, w = 1.0). Tables I–V, listing final atomic parameters for nonhydrogen atoms, coordinate parameters for hydrogen atoms, bond lengths, and bond angles, are given as supplementary material.

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identification of the liverwort and Dr. K. Toriumi of the Institute for Molecular Science for valuable assistance with the X-ray work. Acknowledgement is made to the Institute for Molecular Science for use of a Rigaku four-circle diffractometer. Calculations were performed at the Kyoto University Computing Center and the computer room at the Tokushima Bunri University. Work at the Florida State University was supported in part by a grant (CA-13121) from the United States Public Health Service through the National Cancer Institute.

Registry No. 2, 63599-46-2.

Supplementary Material Available: Tables I–V listing final atomic parameters, bond lengths, and angles (5 pages). Ordering information is given on any current masthead page.

Synthesis of 2-Phenyl-4*H*-thiopyran-4-one

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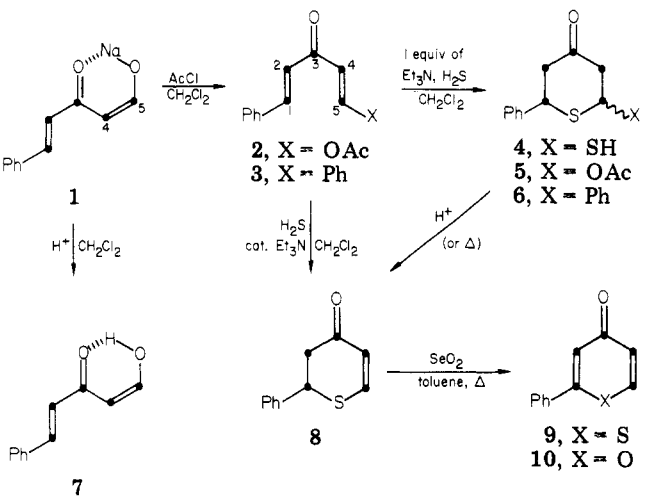
2-Phenyl-4*H*-pyran-4-one (**10**) has been prepared by acid-catalyzed cyclization of the appropriate phenylacetylenic β-keto aldehyde[1] or of (1*E*,4*E*)-5-hydroxy-1-methoxy-5-phenylpenta-1,4-dien-3-one,[2] or via the condensation of the boron difluoride complex of benzoylacetone and dimethylformamide dimethyl acetal.[3] None of these methods, however, is adaptable to the preparation of the thio analogue, 2-phenyl-4*H*-thiopyran-4-one (**9**),[4] which is a key intermediate desired for the synthesis of various *unsymmetrical* $\Delta^{4,4'}$-bis(4*H*-thiopyran) donors[5] with an unsubstituted C-2 position adjacent to sulfur. We now report a method that allows both **9** and its dihydro derivative, **8**, to be readily synthesized from the commercially available methyl styryl ketone.

Formylation of methyl styryl ketone with ethyl formate in the presence of sodium ethoxide in ethanol gave the sodium enolate **1** in 71% yield.[6] The 4*Z* configuration of **1** was established on the basis of its ^{1}H NMR spectrum (Me_2SO-d_6), which has a doublet at δ 4.9 ppm for the C-4 proton with cis coupling of $J_{4,5}$ = 9.75 Hz. Acetylation of **1** with 1 equiv of acetyl chloride in methylene chloride gave the corresponding enol acetate **2** (77% yield), which was assigned the 1*E* and 4*E* stereoconfigurations based on the relatively large, apparent trans H–H coupling constants $J_{1,2}$ = 15.75 and $J_{4,5}$ = 12.75 Hz.[7] (See Scheme I.) The corresponding enol **7**, which was easily prepared by acidification of a methylene chloride suspension of **1** with dilute hydrochloric acid, has a doublet at δ 5.65 ppm for the C-4 proton with cis $J_{4,5}$ = 3 Hz and a doublet at δ 6.45 ppm with a typical trans $J_{1,2}$ = 16.5 Hz as measured.

Scheme I



Compound **2** was not stable to heat. Although **2** could be purified by recrystallization, it was best used immediately without isolation to avoid troublesome decomposition. A solution of the crude enol acetate **2** and a catalytic amount of triethylamine in methylene chloride was saturated with a slow stream of hydrogen sulfide at ambient temperature, giving 5,6-dihydro-6-phenyl-4*H*-thiopyran-4-one (**8**) in 59% yield based on the sodium enolate **1**. This base-catalyzed hydrogen sulfide cyclization of **2** presumably follows the same course as that of 1,5-diphenyl-1,4-pentadien-3-one (**3**) in the preparation of 2,6-diphenyl-4*H*-tetrahydrothiopyran-4-one (**6**).[8] The intermediate, 2-acetoxy-6-phenyl-4*H*-tetrahydrothiopyran-4-one (**5**) formed in situ, apparently was not stable under the experimental conditions, which caused the elimination of acetic acid to produce directly the dihydro derivative **8**. Dehydrogenation of **8** with selenium dioxide in refluxing toluene[9] gave the desired product **9** in 85% yield.

In the presence of 1 equiv of triethylamine, the hydrogen sulfide addition to **2** gave a different product, to which we assigned the structure 2-mercapto-6-phenyl-4*H*-tetrahydrothiopyran-4-one (**4**) on the basis of its spectroscopic data. These include the high-resolution mass spectrum, which shows a molecular ion at *m/e* 224.0343 (calcd for $C_{11}H_{12}OS_2$, 224.0344), and its IR spectrum, which has a $\nu_{C=O}$ at 1710 cm^{-1} that is typical of the carbonyl stretching of a tetrahydro-4*H*-thiopyran-4-one such as **6**.[9] The crude **4**, which has a strong mercaptan odor, was not purified, owing to its lability toward heat, which caused the elimination of hydrogen sulfide to give **8** (shown by the change in the ^{1}H NMR spectrum of **4** heated in an NMR tube at ca. 100 °C). The mercaptan **4** was also unstable toward acid. Thus, on addition of excess trifluoroacetic acid at room temperature, **4** was quickly converted to **8**, which was isolated, upon usual workup, in 55% yield. The formation of **4** from **2** can be attributed to a secondary Michael reaction between the initial product **8** formed in situ and hydrogen sulfide anion, which is present in relatively high concentration. This was confirmed in a separate experiment by treating **8** with excess hydrogen sulfide and 1 equiv of triethylammonium acetate in methylene chloride at room temperature for 24 h, from which 60% of **4** was

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