

rodiphenylmethane on long heating at reflux with SOCl_2 and DMF.

Experimental Section¹²

Reactions with SOCl_2 -DMF. In typical preparative experiments 10.0 g of bisulfite addition compound, or 7.0 g of aldehyde, was added in portions to a stirred mixture of 35 mL of SOCl_2 (pure,¹³ freshly distilled) and 0.5-1.0 mL of DMF held at -10 to -5 °C at all times during preparation. The temperature was allowed to rise slowly and the mixture was stirred for 4 h at room temperature then poured on ice and the products were collected by ether extraction in the cold. The ether layer was washed with saturated salt solution and dried over MgSO_4 . The products (percent yield) were isolated by vacuum distillation. Benzal chloride, **3**, bp 89-90 °C (9.5 mm) (89 or 87% when an equivalent of the bisulfite addition compound was used), was characterized by its NMR spectrum.¹⁴ Dichloro-1-naphthylmethane (91 or 86% from addition compound), bp 106-108 °C (0.5 mm) (lit.¹⁵ bp 146-147 °C (2 mm)), was obtained from **6** and (*E*)-1,1-dichloro-3-phenyl-2-propene, mp 58.0-58.5 °C (lit.¹⁶ mp 57.5-58.5 °C), was obtained from **7**. From **8** a complex mixture of dichlorides was produced in which about 70-75% was estimated to be (*E*)-1,1-dichloro-2-methyl-3-phenyl-2-propene by integration of the NMR peak at δ 5.45 (s, 1) assigned to the CHCl_2 assuming the integration value as $\frac{1}{5}$ of the five ArH (m, 5, δ 7.0-7.5). Both *E* and *Z* forms were present. Because of difficulty in attempted separation and instability of the mixture no C,H analyses were attempted. However, the mass spectra of all fractions had peaks ($M + 1$) at 186, 188, and 190¹² indicating that two chlorine atoms were present.

Kinetic Experiments, Table I. In experiments similar to the above but on a smaller scale with benzaldehyde only the reaction mixture was poured on ice and the entire crude product, isolated as described above, was analyzed by NMR (see Table I). Reagent **5** was prepared by heating 70 mL of SOCl_2 and 0.5 mL of DMF at reflux for $\frac{1}{2}$ h. After cooling to -10 °C 14 g of benzaldehyde was added and aliquots were taken for analysis by the usual method described above. Similar experiments were done on the bisulfite addition compounds.

Dichlorodiphenylmethane. A solution of 4.0 g of benzophenone in 20 mL of SOCl_2 and 0.5 mL of DMF was held at reflux for 16 h. Vacuum distillation yielded 4.4 g (85%) of dichlorodiphenylmethane, bp 98-100 °C (0.5 mm), characterized by its IR spectrum.¹⁴ None of this product was obtained when DMF was omitted. Xanthone and thiazanthone were recovered largely unchanged when DMF was present or absent even on heating at reflux.

Registry No.—**1**, 100-52-7; **3**, 98-87-3; **6**, 66-77-3; **7**, 104-55-2; **8**, 101-39-3; thionyl chloride, 7719-09-7; dimethylformamide, 68-12-2; (*E*)-1,1-dichloro-2-methyl-3-phenyl-2-propene, 67488-96-4; octanal, 124-13-0; cyclohexanone, 108-94-1; acetophenone, 98-86-2; $\text{C}_6\text{H}_5\text{CHOHSO}_3\text{Na}$, 4657-12-9; dichloro-1-naphthylmethane, 17180-26-6; (*E*)-1,1-dichloro-3-phenyl-2-propene, 51157-80-3; (*Z*)-1,1-dichloro-2-methyl-3-phenyl-1-propene, 67488-97-5; benzophenone, 119-61-9; dichlorodiphenylmethane 2051-90-3.

References and Notes

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Use of Dipolar Aprotic Solvents to Alter the Chemoselectivity of Lithium Dimethylcuprate¹

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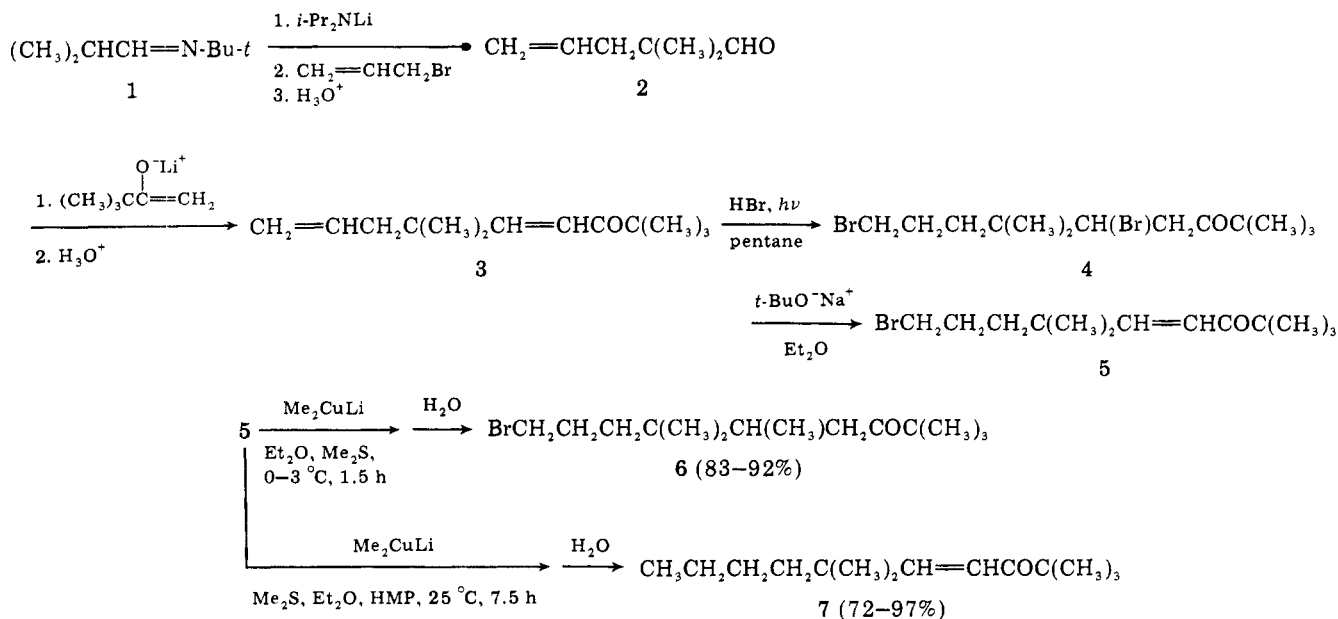
Although the presence of good donor solvents such as THF or HMP [$(\text{Me}_2\text{N})_3\text{PO}$] increases the rate of the displacement reaction at alkyl halides with lithium diorganocuprate reagents,^{2,3} such donor solvents either retard or inhibit the conjugate addition of cuprate reagents to unsaturated carbonyl compounds.⁴ Since the displacement reaction at an alkyl halide and the conjugate addition reaction exhibit opposite responses to added donor solvents, it seemed possible to effect either type of reaction selectively with a cuprate reagent by merely selecting the appropriate reaction solvent. To explore this idea, the bromo enone **5** was prepared by the sequence indicated in Scheme I.

Reaction of this bromo enone **5** with Me_2CuLi in Et_2O - Me_2S solution formed the typical conjugate adduct, bromo ketone **6**, in high yield. This result is not unexpected because conjugate addition reactions of cuprate reagents are typically much faster than displacement reactions at alkyl halides. Since our earlier studies⁴ had indicated that stable solutions of Me_2CuLi could be formed in Et_2O -DMF and that these solutions failed to react with enones having reduction potentials more negative than 2.0 V (vs. SCE), we first examined the reaction of Me_2CuLi with the bromo enone **5** in an Et_2O -DMF mixture. Although the conjugate addition reaction was completely inhibited, the alternative displacement reaction was very slow. After 20 h at 25 °C only 22% of the displacement product **7** was isolated and 75% of the unchanged bromo enone **5** was recovered. Since it was also possible to prepare stable solutions of Me_2CuLi in mixtures of Me_2S , Et_2O , and carefully purified HMP, we also examined the reaction of the bromo enone **5** with Me_2CuLi in this solvent mixture. In this solvent system, the desired conversion of the bromo enone **5** to the methylated enone **7** was complete after 7-8 h at 25 °C and we found no evidence for the presence of any byproduct from conjugate addition. Thus, we conclude that by appropriate choice of reaction medium, it is possible to select only one of the two common synthetic applications of Me_2CuLi , either coupling with a halide or conjugate addition. This same solvent effect is presumably also applicable to other cuprate reagents provided that the cuprate reagents have sufficient thermal stability to allow their use in the relatively slow coupling reaction with an alkyl halide.

Experimental Section⁵

Preparation of the Dibromo Ketone **4 and the Bromo Enone **5**.** Previously described procedures⁶ were employed to prepare the imine **1** and convert it successively to the unsaturated aldehyde **2** and the dienone **3**, bp 38 °C (22 mm), n_D^{25} 1.4617 [lit.⁶ bp 44 °C (25 mm), n_D^{25} 1.4617]. Following a general procedure described earlier,⁷ a solution of 500 mg (2.4 mmol) of the dienone **3** in 250 mL of pentane was flushed with N_2 and then a stream of anhydrous HBr was passed through the solution for 5 min while the solution was irradiated with the light from a 450-W medium-pressure Hg lamp. The pentane solution was again flushed with N_2 and then washed with aqueous $\text{Na}_2\text{S}_2\text{O}_8$, dried, and concentrated. The residual colorless liquid (850 mg) was chromatographed on silica gel with an Et_2O -hexane eluent (1:9 v/v) to separate 377 mg (44%) of the crude dibromide **4** as a white solid, mp 35-37 °C. Recrystallization from hexane separated 339 mg (40%) of the pure dibromide **4** as white needles; mp 46-47 °C; IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 4.55 (1 H, d of d, $J = 2$ and 10 Hz, CH-Br), 3.0-3.6 (3 H, m, BrCH_2 and CHCO), 2.65 (1 H, d of d, $J = 10$ and 17 Hz, CHCO), 1.4-2.2 (4 H, m, CH_2), 1.18 (9 H, s, *t*-Bu), and 1.08 (6 H, s, CH_3); mass spectrum, m/e (rel intensity) 299 (9), 219

Scheme I



(100), 217 (100), 191 (10), 189 (10), 125 (10), 110 (14), 69 (17), 56 (72), and 41 (29).

Anal. Calcd for $\text{C}_{13}\text{H}_{24}\text{Br}_2\text{O}$: C, 43.84; H, 6.79; Br, 44.87. Found: C, 43.77; H, 6.82; Br, 44.86.

In a comparable experiment the crude product from 500 mg (2.4 mmol) of the dienone 3 was distilled under reduced pressure (with accompanying dehydrobromination) to yield 432 mg (65%) of the bromo enone 5 as a colorless liquid: bp 48–52 °C (1 mm), n_{D}^{25} 1.4775; IR (CCl_4) 1685 ($\text{C}=\text{O}$), 1618 ($\text{C}=\text{C}$), and 995 cm^{-1} (trans $\text{CH}=\text{CH}$); UV max (95% EtOH) 229 nm (ϵ 20 500); NMR (CCl_4) δ 6.81 (1 H, d, $J = 16$ Hz, vinyl CH), 6.35 (1 H, d, $J = 16$ Hz, vinyl CH), 3.2–3.6 (2 H, m, CH_2Br), 1.2–2.2 (4 H, m, CH_2), 1.13 (9 H, s, $t\text{-Bu}$), and 1.10 (6 H, s, CH_3); mass spectrum, m/e (rel intensity) 276 (M^+ , 1), 274 (M^+ , 1), 219 (100), 217 (100), 108 (16), 69 (16), and 57 (17).

Anal. Calcd for $\text{C}_{13}\text{H}_{23}\text{BrO}$: C, 56.73; H, 8.42; Br, 29.03. Found: C, 56.82; H, 8.46; Br, 28.93.

In a more satisfactory dehydrobromination procedure, a suspension of 2.41 g (25 mmol) of $t\text{-BuONa}$ in 75 mL of Et_2O was treated with a solution of 5.4 g (15 mmol) of the dibromide 4 in 25 mL of Et_2O and the resulting suspension was stirred at 25 °C for 15 h. After the resulting mixture had been diluted with Et_2O , filtered, and concentrated, the residual crude bromo enone (4.53 g of yellow liquid) was chromatographed on silica gel with an Et_2O -hexane eluent (1:39 v/v) to separate 2.8 g (70%) of the bromo enone 5 as a colorless liquid, n_{D}^{25} 1.4771, that was identified with the previously described sample by comparison of NMR spectra.

Reaction of the Bromo Enone 5 with Me_2CuLi . A. In Et_2O . To a cold (0 °C) solution of Me_2CuLi , from 365 mg (1.78 mmol) of Me_2SCuBr , 3.56 mmol of MeLi (halide free), 8 mL of Et_2O , and 5 mL of Me_2S , was added a solution of 295 mg (1.07 mmol) of the bromo enone 5 in 5 mL of Et_2O . The resulting mixture, from which an orange precipitate separated, was stirred at 0–3 °C for 1.5 h and then siphoned into a cold aqueous solution (pH 8) of NH_3 and NH_4Cl . The ethereal extract of this mixture was dried and concentrated and the residual crude product (0.35 g of yellow liquid) was chromatographed on silica gel with an Et_2O -hexane eluent (1:39 v/v). The bromo ketone 6 was collected as 0.28 g (92%) of colorless liquid: n_{D}^{25} 1.4687; IR (CCl_4) 1710 cm^{-1} ($\text{C}=\text{O}$); ^1H NMR (CCl_4) δ 3.2–3.5 (2 H, m, CH_2Br), 2.2–2.4 (2 H, m, CH_2CO), 1.3–2.1 (5 H, m, aliphatic CH), 1.12 (9 H, s, $t\text{-Bu}$), and 0.7–1.0 (9 H, m, CH_3 including a CH_3 singlet at 0.85); mass spectrum, m/e (rel intensity) 292 (M^+ , 4), 290 (M^+ , 4), 276 (16), 274 (16), 234 (100), 232 (100), 127 (16), 83 (18), 69 (33), 57 (57), 55 (22), 43 (20), and 41 (29); ^{13}C NMR (CDCl_3 , multiplicity in off-resonance decoupling) δ 213.7 (s), 44.0 (s), 38.8 (t), 38.5 (t), 35.2 (t), 34.5 (s), 27.2 (t), 26.2 (q, 5 C atoms), 24.4 (d), and 14.7 (q).

Anal. Calcd for $\text{C}_{14}\text{H}_{27}\text{BrO}$: C, 57.73; H, 9.34; Br, 27.43. Found: C, 57.97; H, 9.39; Br, 27.21.

From a comparable reaction in Et_2O at 0–5 °C for 2 h, the yield of the bromo ketone 6 was 83%.

B. In Et_2O -HMP. Before use commercial hexamethylphosphoramide (HMP, Fisher Scientific Co.) was refluxed under reduced pressure (60 °C at 0.5 mm) over BaO for 1 h and then distilled from

BaO under reduced pressure [bp 55–60 °C (0.4–0.5 mm)]. During this distillation a substantial forerun (ca. 30 mL) was discarded and especial care was taken to avoid exposure of the purified solvent to either H_2O or O_2 . To a solution of Me_2CuLi , from 365 mg (1.78 mmol) of Me_2SCuBr , 3.56 mmol of MeLi (halide free), 6 mL of Me_2S , and 8 mL of ether, was added 15 mL of freshly purified HMP. To the resulting colorless solution was added, dropwise and with stirring, a solution of 295 mg (1.07 mmol) of the bromo enone 5 in 5 mL of Et_2O . The resulting solution was stirred at 25 °C for 7.5 h during which time the solution slowly turned dark yellow in color but no precipitate separated. The reaction mixture was siphoned into a cold aqueous solution (pH 8) of NH_3 and NH_4Cl and extracted with Et_2O . The ethereal extract was washed with H_2O , dried, and concentrated to leave a yellow liquid (a mixture of product and HMP). Chromatography on silica gel with an EtOAc -hexane eluent (1:65 v/v) separated 0.22 g (97%) of the enone 7 as a colorless liquid: n_{D}^{25} 1.4536; IR (CCl_4) 1690 (conj $\text{C}=\text{O}$) and 1620 cm^{-1} ($\text{C}=\text{C}$); UV max (95% EtOH) 229 nm (ϵ 8600); ^1H NMR (CCl_4) δ 6.80 (1 H, d, $J = 14$ Hz, vinyl CH), 6.33 (1 H, d, $J = 14$ Hz, vinyl CH), and 0.7–1.5 (24 H, m, aliphatic CH including a $t\text{-Bu}$ singlet at 1.16 and a CH_3 singlet at 1.07); mass spectrum, m/e (rel intensity) 210 (M^+ , 2), 153 (100), 69 (58), 57 (53), 55 (29), 41 (45), and 39 (52); ^{13}C NMR (CDCl_3 , multiplicity in off-resonance decoupling) δ 202.8 (s), 155.6 (d), 119.6 (d), 42.7 (s), 42.0 (t), 36.5 (s), 26.7 (t), 26.5 (q, 2 C atoms), 26.2 (q, 3 C atoms), 23.3 (t), and 14.0 (q).

Anal. Calcd for $\text{C}_{14}\text{H}_{26}\text{O}$: C, 79.93; H, 12.46. Found: C, 79.78; H, 12.42.

In three comparable experiments employing a mixture of Et_2O , Me_2S , and HMP as the reaction solvent with reaction times of 8–20 h at 22–25 °C, the isolated yields of enone 7 were 72, 78, and 80%. In a similar experiment, a solution of 1.09 mmol of Me_2CuLi and 0.72 mmol of the bromo enone 5 in 6 mL of Me_2S , 9.4 mL of Et_2O , and 15 mL of DMF [freshly distilled, bp 43 °C (16 mm)] was stirred at 23 °C for 20 h and subjected to the usual isolation procedure. By use of preparative TLC (silica gel coating with an Et_2O -hexane eluent, 1:4 v/v), 34 mg (22%) of the enone 7 (R_f 0.78) and 151 mg (75%) of the starting bromo enone 5 (R_f 0.70) were isolated.

Registry No.—3, 67489-20-7; 4, 67489-21-8; 5, 67489-22-9; 6, 67489-23-0; 7, 67489-24-1; lithium dimethylcuprate, 15681-48-8.

References and Notes

- (1) This research has been supported by Public Health Service Grant R01-GM-20197 from the National Institute of General Medical Science. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.
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otherwise stated MgSO_4 was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary, Model 14, or a Perkin-Elmer, Model 202, recording spectrophotometer. The proton NMR spectra were determined at 60 MHz with a Varian, Model A-60 or Model T-60-A, NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer, Model RMU-7, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

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Structural Studies on Juncusol. A Novel Cytotoxic 9,10-Dihydrophenanthrene Derivative from the Marsh Plant *Juncus roemerianus*¹

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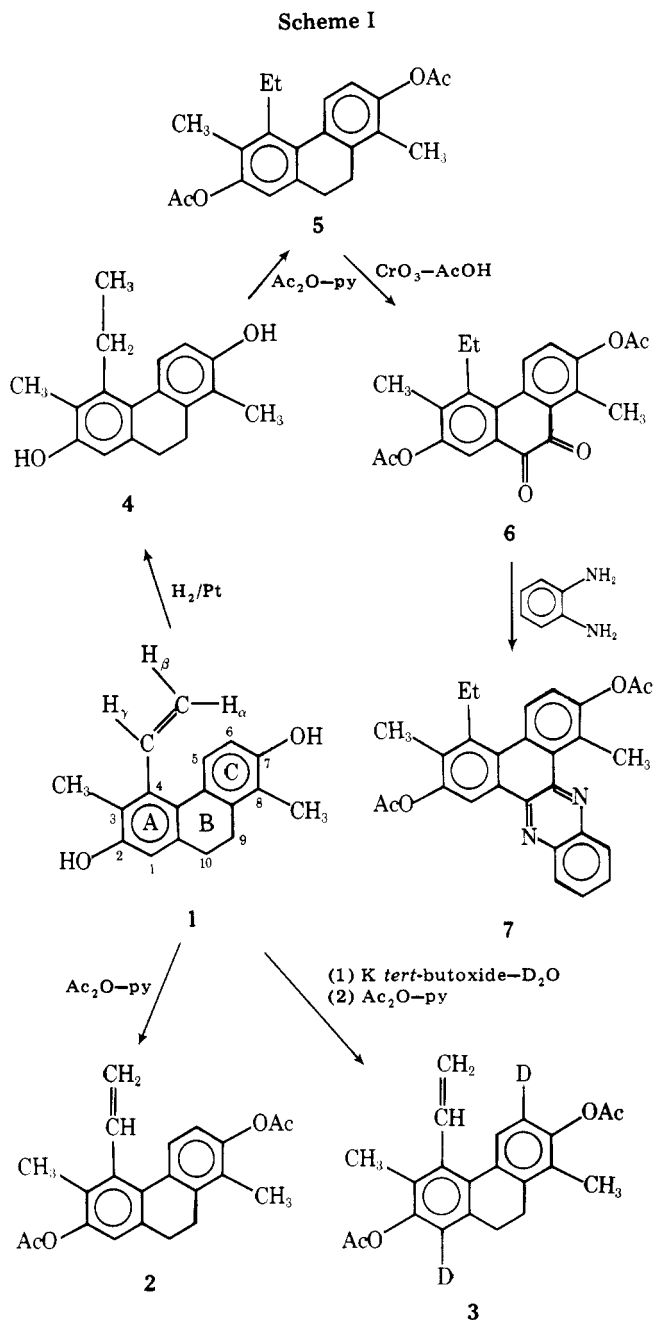
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Juncus roemerianus (NO Juncaceae) is the most dominant among a group of plants, commonly known as "marsh grass", which grow abundantly on and near the coastal areas of the southeastern United States. An earlier report³ indicated that 95% of the organic matter produced in the marsh is not attacked by the marsh herbivores, but on death and decomposition the plants enter the detritus food chain. A 95% ethanolic extract of the tops of *J. roemerianus* showed activity against P 388 lymphocytic leukemia in BDF₁ mice.⁴ A preliminary study on the volatile constituents of *J. roemerianus* was reported earlier from our laboratory.⁵ To our knowledge no detailed chemical investigation of *J. roemerianus* or any other marsh grass had been reported in the literature prior to our work. The CHCl_3 extract of the tops of this plant, upon chromatography over silica gel, yielded, inter alia, the cytotoxic⁶ compound juncusol, $\text{C}_{18}\text{H}_{18}\text{O}_2$, mp 175–176 °C. Recently we reported⁷ the structure of juncusol diacetate based on an X-ray crystallographic study. We now wish to report an extensive chemical and spectral study of juncusol and its derivatives in support of the structure of juncusol as 1 (Scheme I). Although about 20 of the relatively rare 9,10-dihydrophenanthrene derivatives are known from nature,⁸ juncusol is unique in possessing an alkenyl substituent in the ring system in addition to rarely encountered alkyl groups. Juncusol, like all other members of its class, is a phenol, but unlike others it does not contain a methoxyl substituent.

Results and Discussion

The finely ground plant tops (above ground) of *J. roemerianus* were extracted with chloroform. The concentrated chloroform extract was triturated with chloroform–benzene (1:1). Chromatography of the soluble portion on silica gel followed by crystallization from benzene yielded (0.01% dry weight) juncusol, $\text{C}_{18}\text{H}_{18}\text{O}_2$ (M^+ at m/e 266), mp 175–176 °C. The IR spectrum of juncusol (1) in KBr exhibits peaks at 3350 (OH), 1603 (aromatic), 930 (vinyl), and 870 and 830 (two adjacent Ar–H) cm^{-1} . The UV spectrum in ethanol shows λ_{max} at 247 sh, 266 sh, 284 sh ($\log \epsilon$ 4.12), and 318 sh nm, characteristic of the 9,10-dihydrophenanthrenes. A typical 4 H singlet at δ 2.50 in the ^1H NMR spectrum of juncusol confirms^{9,10}



its 9,10-dihydrophenanthrene skeleton. The 100 MHz NMR spectrum of juncusol in CDCl_3 (with a few drops of acetone- d_6) also shows sharp singlets at δ 2.26 (3 H, Ar- CH_3) and 2.31 (3 H, Ar- CH_3), ABX type of signals for a vinyl group consisting of three sets of "quartets" at δ 5.20 (1 H, $J_{\text{AX}} = 18$ Hz and $J_{\text{AB}} = 2$ Hz), 5.46 (1 H, $J_{\text{BX}} = 11$ Hz and $J_{\text{AB}} = 2$ Hz), and 6.78 (1 H, $J_{\text{AX}} = 18$ Hz and $J_{\text{BX}} = 11$ Hz), two ortho aromatic proton doublets at δ 6.66 ($J = 8$ Hz) and 7.50 ($J = 8$ Hz), and an aromatic proton singlet at δ 6.70. The relative low field shift of one of the aromatic proton doublets at δ 7.50 indicates it to be at C-5 (or C-4) of the 9,10-dihydrophenanthrene ring system. Therefore, the ortho aromatic protons must be present at C-5 and C-6 and the remaining proton must be in ring A in juncusol. In the ^1H NMR spectrum of juncusol in pyridine- d_5 , the CH_3 groups shift to δ 2.51 ($\delta_{\text{pyridine}} - \delta_{\text{chloroform}} = 0.25$ ppm) and 2.62 ($\delta_{\text{pyridine}} - \delta_{\text{chloroform}} = 0.31$ ppm), the C-6 aromatic proton shifts to δ 7.07 ($\delta_{\text{pyridine}} - \delta_{\text{chloroform}} = 0.41$ ppm), and the ring A aromatic proton singlet shifts to δ 7.10 ($\delta_{\text{pyridine}} - \delta_{\text{chloroform}} = 0.40$ ppm). These significantly large pyridine-induced solvent shifts to lower fields can only be attributed to the orientations of the CH_3 groups and the aromatic protons in question being ortho to the OH groups.¹¹