Synthesis of (Z)-6-Heneicosen-11-one. Douglas Fir Tussock Moth Sex Attractant

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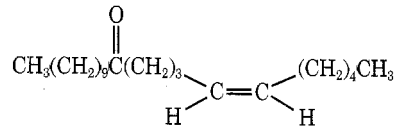
Received November 29, 1974

The syntheses of (Z)-6-heneicosen-11-one, the principal component of the sex attractant of the Douglas fir tussock moth, and the corresponding E isomer are described. The stereochemistries of the products were determined by selective reductions of the common intermediate, 6-heneicosyn-11-ol. The lower limits of isomeric purity of the products, determined by gas chromatographic analysis of the corresponding epoxides, was >97 and >98% for the Z and E isomers, respectively.

Chemical and spectroscopic studies of the sex attractant of the Doublas fir tussock moth (*Orgyia pseudotsugata*), a severe defoliator of firs in western North America, have led to the isolation and identification of (Z)-6-heneicosen-11-one (1) which is highly attractive in laboratory and field tests.[1] In the course of this work it became necessary to synthesize both 1 and the corresponding E isomer, 2, to establish the stereochemistry of the natural attractant and to provide synthetic material for entomological testing.



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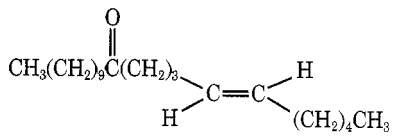
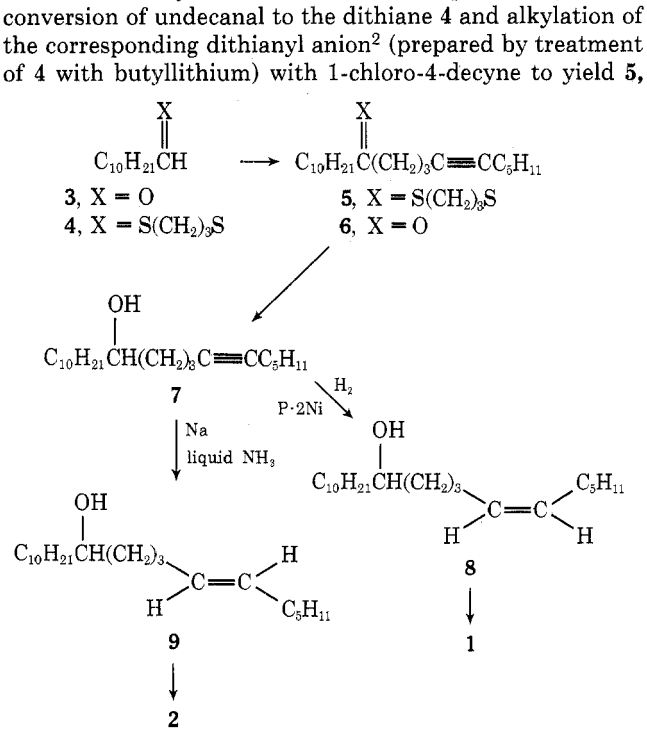
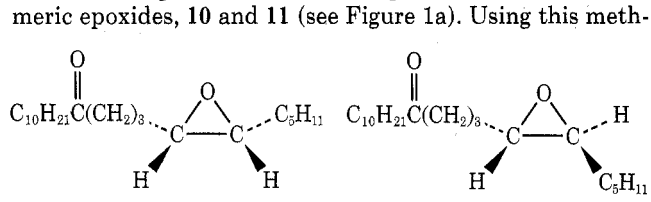


2

Synthesis. Both 1 and 2 were prepared from the acetylenic ketone 6. Synthesis of 6 was accomplished by initial conversion of undecanal to the dithiane 4 and alkylation of the corresponding dithianyl anion[2] (prepared by treatment of 4 with butyllithium) with 1-chloro-4-decyne to yield 5, which was hydrolyzed, restoring the carbonyl group. Conversion of 6 to the isomeric olefins, 1 and 2, involved initial reduction of the carbonyl to obtain the acetylenic alcohol, 7, which was subjected to the appropriate stereospecific method of acetylene reduction. Catalytic reduction of 7 using P-2 nickel poisoned with ethylenediamine[3] yielded the Z olefinic alcohol 8 whereas the isomeric E olefinic alcohol was prepared by treatment of 7 with sodium in liquid ammonia.[4] Finally, reoxidation of the isomeric alcohols (8 and 9) yielded the corresponding ketones 1 and 2.



Stereochemical Analysis. The stereochemistries of the Z and E olefinic ketones, 1 and 2, were confirmed by infrared spectroscopy. The spectrum of 2 exhibited a sharp band at 10.4 μ (absent in the spectrum of 1), characteristic of E-disubstituted olefins.[5] Since stereochemical purity is critical for the function of several known insect pheromones,[6,7] it was necessary to obtain a quantitative measure of isomeric purity in the products 1 and 2. Gas–liquid chromatographic (GLC) separation of the stereoisomers 1 and 2 was unsuccessful using a variety of polar phases in packed columns.[8] In previous instances where direct GLC separation of E and Z isomers of long-chain monounsaturated olefins was difficult, analysis was achieved by examination of the corresponding epoxides.[6,9] The results in the present case are similar. Ketones 1 and 2 were readily epoxidized using *m*-chloroperbenzoic acid and GLC conditions were found which gave near-baseline separation of the two isomeric epoxides, 10 and 11 (see Figure 1a). Using this method the Z isomer (10) was shown to be >97% pure (Figure 1b) and the E isomer (11) was >98% pure (Figure 1c). These numbers represent lower limits of stereochemical purity of the ketones 1 and 2, since any isomerization occurring during the epoxidation reaction or work-up procedure would result in lower isomeric purity in the corresponding epoxides.



10 11

Experimental Section

Melting ranges were taken with a Thomas-Kofler micro hot stage. NMR spectra were obtained in CCl_4 (Me_4Si internal standard) using a Varian HA-100 spectrometer, infrared spectra were recorded on a Perkin-Elmer 337, and mass spectra were measured using either a CEC 21-110B or Du Pont 21-491B spectrometer. Analyses were by the Heterocyclic Chemical Corp., Harrisonville,

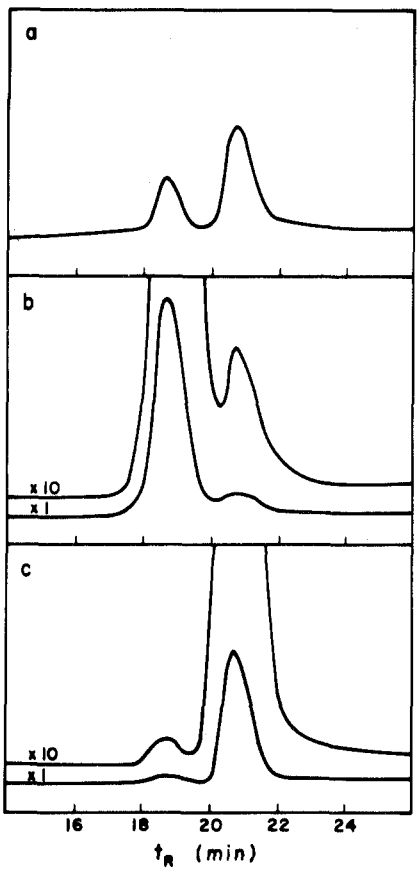


Figure 1. Gas chromatographs of epoxidation products derived from (a) a 1:2 mixture of **1** and **2**, (b) **1**, and (c) **2**.

Mo. Chromatographic separations were achieved with benzene on an alumina (activity III) column (40 × 2 cm) using the dry-column method.[10] Gas–liquid chromatographic (GLC) analyses (other than the stereochemical determinations) were obtained using a Varian 1200 gas chromatograph equipped with a 4 ft × 0.25 in. column of 3% Dexsil 300 on 80/100 Chromosorb W, AW-DMCS.

2-*n*-Decyl-1,3-dithiane (4). Using a procedure similar to that of Fieser,[11] 10 ml of boron trifluoride etherate was slowly added to a flask containing 51 g (0.3 mol) of undecanal (Chemical Samples Co.) and 32.4 g (0.3 mol) of 1,3-propanedithiol. After stirring for 1 hr the resulting two-phase mixture was added to 100 ml of water and extracted with two 50-ml portions of benzene. The combined benzene extracts were washed with four 50-ml portions of 3% aqueous sodium hydroxide and one 50-ml portion of water before drying over anhydrous magnesium sulfate. Evaporation of the solvent left 81 g of light-yellow liquid. Distillation at 125–128° (0.01 mm) gave 76.5 g (98%) of **4** as a colorless liquid: NMR δ 2.78 (m, 4 H, $-SCH_2$), 3.95 (t, 1 H, –SCH); mass spectrum (70 eV) *m/e* (rel intensity) 260 (44, $M\cdot^+$), 185 (33, $C_{10}H_{21}C{\equiv}S^+$), 119 (100, –S–C^+H–S–).

Anal. Calc'd. for $C_{14}H_{28}S_2$: C, 64.61; H, 10.77. Found: C, 64.59; H, 11.01.

11-Propylenedithio-6-heneicosyne (5). Following the procedure described by Corey,[12] 92 ml of 2.0 *M* *n*-butyllithium (in hexane) was added to a solution of 40.0 g (154 mmol) of **4** in 300 ml of freshly distilled (over CaH_2) tetrahydrofuran, cooled to −20°. This solution was stirred under nitrogen for 1.5 hr before adding 31.6 g (184 mmol) of 1-chloro-4-decyne[13] (Chemical Samples Co.). After sitrring for an additional 3 hr at −20° the reaction solution was allowed to stand for 60 hr at −10°. The reaction solution was added to a solution of 20 ml of acetic acid in 200 ml of water and extracted with four 75-ml portions of hexane. The combined hexane extracts were washed with three portions of 100 ml of saturated aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate, and the solvent was evaporated to leave 52.0 g of a yellow liquid containing (by GLC) 10% unreacted starting material **4**. A sample of this product was purified by distillation at 176–178° (0.01 mm) to give a colorless liquid: NMR δ 2.78 (m, 4 H, $-SCH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 396 (21, $M\cdot^+$), 363 [10, $(M - SH)^+$], 321 [83, $(M - CH_2CH_2CH_2SH)^+$], 290 [65, $(M - HSCH_2CH_2CH_2SH)\cdot^+$], 259 [54, $(M - C_{10}H_{17})^+$], 119 (100, –S–C^+H–S–).

Anal. Calcd for $C_{24}H_{44}S_2$: C, 72.73; H, 11.11. Found: C, 72.88; H, 11.33.

6-Heneicosyn-11-one (6). A 30.9-g (78 mmol) sample of **5** (undistilled) was hydrolyzed by the method of Narasaka et al.[14] using 24.8 g (0.312 mol) of cupric oxide and 26.6 g (0.156 mol) of cupric chloride dihydrate in 500 ml of acetone and 5 ml of water. From this reaction was isolated 21.5 g (90%) of **6** as a light yellow liquid, bp 164–167° (0.01 mm), which slowly crystallized to a waxy solid: ir (melt) 5.84 μ (C=O); NMR δ 2.00–2.23 (m, 4 H, $C{\equiv}CCH_2$), 2.25–2.60 (m, 4 H, $CH_2C{=}O$); mass spectrum (70 eV) *m/e* (rel intensity 306 (100, $M\cdot^+$), 169 [74, $(M - C_{10}H_{17})^+$], 165 [20, $(M - C_{10}H_{21})^+$], 122 [42, $(C_5H_{11}C{\equiv}CCH{=}CH_2)\cdot^+$].

Anal. Calcd for $C_{21}H_{38}O$: C, 82.35; H, 12.42. Found: C, 82.41; H, 12.51.

6-Heneicosyn-11-ol (7). A solution of 1.33 g (35 mmol) of lithium aluminum hydride in 300 ml of anhydrous ether was prepared under nitrogen. To this stirred solution was added a solution of 21.0 g (69 mmol) of **6** in 50 ml of anhydrous ether. Stirring was continued for 1.5 hr before destroying excess hydride with slow addition of 5% aqueous sodium hydroxide. The mixture was filtered, the filtrate was dried over anhydrous magnesium sulfate, and the solvent was evaporated to produce 17.3 g of a yellow liquid. Separation by column chromatography afforded 14.2 g (67%) of GLC-pure **7** as a colorless liquid: bp 150–152° (0.01 mm); ir (neat) 3.01 μ (broad, –OH); NMR δ 1.98–2.25 (m, 4 H, $C{\equiv}CCH_2$), 3.52 (m, 1 H, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 308 (1, $M\cdot^+$), 290 [1, $(M - H_2O)\cdot^+$], 167 (100, $C_{10}H_{17}CH{=}{}^+OH$).

Anal. Calcd for $C_{21}H_{40}O$: C, 81.82; H, 12.99. Found: C, 81.69; H, 13.02.

(*Z*)-6-Heneicosen-11-ol (8). A 1.0-g (3.25 mmol) sample of **7** was catalytically hydrogenated using P-2 nickel poisoned with ethylenediamine as described by Brown and Ahuja.[3] Upon filtration and evaporation of solvent, the isolated product, **8**, weighed 0.90 g (89%): ir (neat) 3.01 μ (broad, –OH), no band at 10.4 μ (*E*-disubstituted olefin); NMR δ 2.00 (m, 4 H, allylic), 3.46 (m, 1 H, CHO), 5.30 (m, 2 H, vinyl); mass spectrum (70 eV) *m/e* (rel intensity) 310 (1, $M\cdot^+$), 292 [2, $(M - H_2O)\cdot^+$], 124 (100, $(C_5H_{11}CH{=}CHCH{=}CH_2)\cdot^+$].

Anal. Calcd for $C_{21}H_{42}O$: C, 81.28; H, 13.63. Found: C, 81.09; H, 13.81.

(*Z*)-6-Heneicosen-11-one (1). Using the procedure described by Ratcliffe and Rodehorst,[15] a 0.615-g (2.0 mmol) sample of **8** was oxidized by addition to a stirred mixture of 1.8 g (18 mmol) of chromium trioxide and 2.85 g (36 mmol) of pyridine in 50 ml of methylene chloride. The worked up product[15] was chromatographed to obtain 0.53 g (86%) of **1** as a colorless liquid: ir (neat) 5.82 μ (sharp, C=O), no C–H band at 10.4 μ (*E*-disubstituted olefin); NMR δ 2.00 (m, 4 H, allylic), 2.30 (t, 4 H, $-CH_2C{=}O$), 5.29 (m, 2 H, vinyl); mass spectrum (70 eV) *m/e* (rel intensity) 308 (5, $M\cdot^+$), 197 [25, $C_{10}H_{21}CO^+(CH_2)_2-$], 169 (29, $C_{10}H_{21}C{\equiv}O^+$), 167 (23, $C_{10}H_{19}C{\equiv}O^+$], 124 [100, $(C_5H_{11}CH{=}CHCH{=}CH_2)\cdot^+$].

Anal. Calcd for $C_{21}H_{40}O$: C, 81.82; H, 12.99. Found: C, 81.90; H, 13.18.

(*E*)-6-Heneicosen-11-ol (9). A solution of 5.0 g (16.0 mmol) of **7** in 75 ml of anhydrous ether was added to a solution of about 0.95 g of metallic sodium in 250 ml of liquid ammonia.[4] Vigorous stirring was required for 43 hr before quenching with 5 ml of a saturated aqueous ammonium chloride solution. The ammonia was evaporated and the remaining residue was added to 50 ml of hexane, extracted with two 50-ml portions of water, dried over anhydrous magnesium sulfate, and filtered, and the hexane was evaporated to yield 4.7 g (95%) of **9**: mp 40–42°; ir (melt) 3.04 μ (broad, –OH), 10.4 μ (sharp, C–H bending for *E*-disubstituted alkene); NMR δ 1.85–2.30 (m, 5 H, allylic H and hydroxyl H), 3.50 (m, 1 H, CHO), 5.36 (m, 2 H, vinyl); mass spectrum (70 eV) *m/e* (rel intensity) 310 (1.3, $M\cdot^+$), 124 [100, $(C_5H_{11}CH{=}CHCH{=}CH_2)\cdot^+$].

Anal. Calcd for $C_{21}H_{42}O$: C, 81.28; H, 13.63. Found: C, 81.03; H, 13.81.

(*E*)-6-Heneicosen-11-one (2). A 3.0-g (10 mmol) sample of **9** was oxidized as described for the *Z* isomer to obtain 2.2 g (71%) of **2** as a white solid: mp 36–38°; ir (melt) 5.89 μ (C=O), 10.41 μ (sharp, C–H bending for *E*-disubstituted alkene); NMR δ 1.95 (m, 4 H, allylic), 2.26 (t, 4 H, $CH_2C{=}O$), 5.30 (m, 2 H, vinyl); mass spectrum (70 eV) *m/e* (rel intensity) 308 (25, $M\cdot^+$), 197 [28, $C_{10}H_{21}CO^+(CH_2)_2-$], 169 (68, $C_{10}H_{21}C{\equiv}O^+$), 167 (25, $C_{10}H_{19}C{\equiv}O^+$ 124 [100, $(C_5H_{11}CH{=}CHCH{=}CH_2)\cdot^+$].

Anal. Calcd for $C_{21}H_{40}O$: C, 81.82; H, 12.99. Found: C, 81.71; H, 13.19.

***cis*-Heneicosan-6,7-epoxy-11-one (10).** To a 0.45-g (1.46 mmol) sample of 1 dissolved in 20 ml of methylene chloride was added 0.504 g (2.92 mmol) of *m*-chloroperbenzoic acid which was stirred into solution before refrigerating at 5° for 15 hr.

The reaction mixture was transferred to a separatory funnel, 1.0 ml of dimethyl sulfide was added to destroy excess peracid, and the mixture was extracted with three 20-ml portions of saturated aqueous sodium bicarbonate solution and one 20-ml portion of water. The clear solution was dried over anhydrous magnesium sulfate and filtered, and the methylene chloride was removed. A 5-mg sample of this product was dissolved in methylene chloride for isomeric analysis. The remaining material was chromatographed, decolorized with activated charcoal, and recrystallized once from benzene–hexane to yield 0.23 g (48%) of **10:** mp 29–36°; ir (CCl_4 solution) 5.84 μ (C=O); NMR δ 2.35 (m, 4 H, CH_2C=O), 2.70 (m, 2 H, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 324 (19, $M^{\cdot+}$), 169 (42, $C_{10}H_{21}C{\equiv}O^+$), 156 [100, $(C_5H_{11}\overline{CHCHO}CH_2CH_2CH_2 + H)^{\cdot+}$].

Anal. Calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 78.05; H, 12.33.

***trans*-Heneicosan-6,7-epoxy-11-one (11).** A 1.0-g (3.24 mmol) sample of **2** was epoxidized with 1.12 g (6.48 mmol) of *m*-chloroperbenzoic acid using the same procedure as described for the *Z* isomer. Isomeric analysis of this product was performed on a 5-mg sample before column chromatography and recrystallization from benzene–hexane. The remainder of the product, after one recrystallization, weighed 0.54 g (51%): mp 92–97°; ir (CCl_4 solution) 5.82 μ (C=O); NMR δ 2.30 (m, 4 H, CH_2C=O), 2.46 (m, 2 H, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 324 (19, $M^{\cdot+}$), 169 (42, $C_{10}H_{21}C{\equiv}O^+$), 156 [100, $(C_5H_{11}\overline{CHCHO}CH_2CH_2CH_2 + H)^{\cdot+}$].

Anal. Calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 77.51; H, 12.42.

Stereochemical Analyses. Samples of **10, 11,** and a 1:2 mixture of **10** and **11** (all in methylene chloride solutions) were examined using a Varian 2700 gas chromatograph equipped with dual flame ionization detectors and a 12 ft × 0.125 in. stainless steel column packed with 10% Apolar 10C on 100/120 mesh Gas-Chrom Q (Applied Science Laboratories). After conditioning overnight at 260° the column was set isothermally at 165°. At this temperature the two isomers, **10** and **11,** were eluted at 19 and 21 min, respectively,[16] with near-baseline resolution (see Figure 1a). The detector output was recorded on two channels of a Gould Brush 260 recorder, the two channels differing in sensitivity by a factor of 10. This made it possible to measure and compare the peak areas of both isomers from a single injection. Duplicate runs were made for each isomer. Measurements of peak areas using peak height and width at half height show the *Z* isomer to be 97.60 and 97.63% pure and the *E* isomer to be 98.42 and 98.49% pure. Calculations using (1) a planimeter and (2) weights of cut-out peaks from photocopies of chromatograms gave values which do not differ by more than 0.3%.

Acknowledgment. Financial assistance was provided by U.S. Forest Service Pacific Northwest Forest and Range Experiment Station, Northwest Forest Pest Action Council, and State of Washington, Department of Natural Resources.

Registry No.—**1,** 54844-65-4; **2,** 54844-66-5; **4,** 54844-67-6; **5,** 54844-68-7; **6,** 54844-69-8; **7,** 54844-70-1; **8,** 54844-72-2; **9,** 54844-72-3; **10,** 54844-73-4; **11,** 54844-74-5; undecanal, 112-44-7; 1,3-propanedithiol, 109-80-8.

References and Notes

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(16) The GLC retention times of a *Z* olefin and its epoxide are typically greater than those of the corresponding *E* isomers.[6,9] The reverse order in the present case is unexplained.

Fungal Extractives. IX.[1a] Synthesis of the Velleral Skeleton[1b] and a Total Synthesis of Pyrovellerolactone

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Received December 17, 1974

A synthetic route to the skeleton of the hydroazulenic sesquiterpene velleral (1) (from *Lactarius vellereus* and *L. Pergamenus;* Russulaceae, basidiomycetes) is described. The key intermediate 2,2,4-trimethylfuro[6,7-*c*]perhydroazulene (**13**) was transformed to the maleic anhydride derivative **18** by anodic oxidation of the furan ring to the corresponding 2,5-dihydroxy-2,5-dihydrofuran **17** followed by Jones oxidation. Two crystalline maleimides (**22** and **23**) were prepared for X-ray analysis by reaction of **18** with *p*-bromoaniline and **13** with *N*-(*p*-bromophenyl)maleimide. A $Eu(fod)_3$-induced chemical shift analysis was used to determine the stereostructure of 1,8,8-trimethylfuro[3,4-*c*]bicyclo[4.3.1]decan-10-ol (**7**). Hydrogenation of velleral gave a stereoisomer of **13**. A molecular force field calculation was used to determine the most stable conformer of a model precursor to **13**. A total synthesis of pyrovellerolactone (**3**) was accomplished using a new method for the preparation of lactones from furans (electrochemical oxidation followed by hydrolysis).

During the last few years we have reported seven new sesquiterpenes from basidiomycetes of the genus *Lactarius.* Of these, isovelleral[1c] has the same basic skeleton as marasmic acid,[2] which has been the object of synthetic work by other groups;[3,4] lactaral,[5] a 4-substituted furan-3-aldehyde with a previously unknown carbon skeleton, has recently been synthesized by us;[6] the remaining five sesquiterpenes [velleral (**1**),[7] vellerolactone (**2**),[8,9] pyrovellerolactone (**3**),[8,9] and two furan alcohols[10]) have a hydroazulenic skeleton with a *gem*-dimethyl-substituted cyclopentane