Improved Synthesis of 2-Methyl-6-methylene-2,7-octadien-4-ol, a Pheromone of *Ips paraconfusus*, and an Alternative Synthesis of the Intermediate, 2-Bromomethyl-1,3-butadiene

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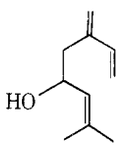
The objective of this study was to prepare 2-methyl-6-methylene-2,7-octadien-4-ol (**1**), a principal component of



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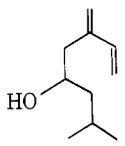

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the aggregation pheromone of *Ips paraconfusus* Lanier (*confusus*), a bark beetle.[1]

Unsuccessful attempts have been made to synthesize **1** and **2** (2-methyl-6-methylene-7-octen-4-ol, another component of the pheromone of *Ips paraconfusus*) by coupling 3-methyl-2-butenal or isovaleraldehyde with either the Grignard reagent or the lithium salt of 2-bromomethyl-1,3-butadiene (**4a**). Both molecules were synthesized by a route involving the reaction of **4a** with the propane dithioketal anions of the respective aldehydes.[2] In both cases, the yield of alcohol was low. Vig, *et al.*,[3] has reported the synthesis of **2** in low yield and, most recently, Katzenellenbogen and Lenox[4] have synthesized **2** from the reaction of **4a** with zinc and isovaleraldehyde in THF in 52% yield. We wish to report the synthesis of **1** by the latter method.

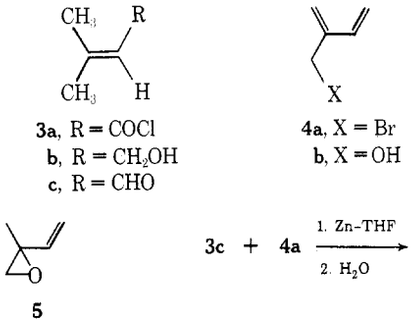
The precursor aldehyde, 3-methyl-2-butenal (**3c**), was synthesized by conversion of 3-methyl-2-butenoic acid to its acid chloride **3a** (98%), lithium aluminum hydride reduction of **3a** to 3-methyl-2-buten-1-ol (**3b**, 85%), and oxidation of **3b** with chromium trioxide–pyridine in methylene chloride to **3c** (48%).[5]

Attempted selective reduction of **3a** with $LiAlH(O\text{-}t\text{-}Bu)_3$ produced compound **3b** in low yield. Treatment of **3b** with CrO_3 on graphite[6] (Seloxcette) in pentane, hexane, or benzene gave a mixture of **3b**, **3c** (40% in the best experiment), and polymer.

2-Bromomethyl-1,3-butadiene (**4a**) was synthesized by the method of Krug and Yen[7] in 18% overall yield. Alternatively, compound **4a** can be synthesized by rearrangement of 3-methyl-3,4-oxido-1-butene (**5**, prepared from isoprene by the method of Reist, Junga, and Baker[8]) to 2-hydroxymethyl-1,3-butadiene (**4b**) with lithium diisopropylamide,[9] followed by bromination with phosphorus tribromide in ether. The convenience of this sequence compensates for its lower over-all yield (11%). Reaction of **3c** and **4a** with zinc in refluxing tetrahydrofuran followed by hydrolysis gave **1** in 65% yield after distillation (see Scheme I).

Caution! Distillation temperatures in excess of 100° should be avoided. Attempted distillation of **1** (>100°, 30 mm) produced *trans*-2-methyl-6-methylene-3,7-octadien-2-ol (ir and nmr identical with those reported by Silverstein, *et al.*[10]) and a mixture of tetraenes (dehydration products), *m/e* 136 (M^+), as major side products. Prolonged high temperature polymerizes the compound. Distillation conditions have been determined that give the alcohol in high purity (>95% by glc analysis).

Scheme I



Experimental Section

Reagents. 3-Methyl-2-butenoic acid (Aldrich) and 3-methylsulfolene (Chemicals Procurement Laboratories, Inc.) were used without further purification. Chromic anhydride was dried under vacuum over P_2O_5 and methylene chloride was purified by the method of Ratcliffe.[5] Pyridine was dried by distillation over barium oxide. The pyridine and THF were stored over 4A molecular sieves.

Methods. Nuclear magnetic resonance spectra were obtained with Varian A-60 and XL-100 spectrometers on $CDCl_3$ solutions (except where noted) with TMS as an internal standard. Infrared spectra were obtained with Perkin-Elmer Model 137 and 621 spectrophotometers, and mass spectra with a Hitachi RMU-6 spectrometer. The purities of some intermediates and the target molecule were determined with a Varian Model 1740 gas chromatograph fitted with flame ionization detectors and a splitter with a split ratio of 100:1. The following glc columns were used: column A, 4% Carbowax 20M on Chromosorb G 60/80 mesh (stainless steel), 5 ft × 0.125 in., He flow rate 30 cm^3/min, column temperature 75°; column B, 5% Carbowax 20M on Chromosorb G 60/80 mesh (glass), 20 ft × 0.25 in., He flow rate 50 cm^3/min, column temperatures 80 and 140°, injection temperatures 100 and 140° respectively; column C, 5% diethylene glycol succinate on chromosorb W 80/100 mesh (stainless steel). 15 ft × 0.125 in., N_2 flow rate 30 cm^3/min, column temperature 150°. Carbon–hydrogen analyses were performed by Microanalysis Inc., Wilmington, Del. All boiling points are uncorrected.

3-Methyl-2-buten-1-ol (3b). To 50 g (0.5 mol) of 3-methyl-2-butenoic acid was added dropwise, over a period of 0.5 hr, 89.25 g (0.74 mol) of thionyl chloride. Following addition, the stirred mixture was allowed to warm to room temperature over a period of 1 hr. The excess thionyl chloride was removed and the product was distilled, yield 55.8 g (94%) of **3a**: bp 43–44° (15 mm); nmr δ 6.10 (m, 1 H, olefinic), 2.14 (d, 3 H, J = 1 Hz, CH_3), 1.96 (d, 3 H, J = 1.5 Hz, CH_3). An ether solution of 27.44 g (0.231 mol) of **3a** was added dropwise over a period of 2 hr to a rapidly stirred solution of 8.76 g (0.231 mol) of $LiAlH_4$ in dry ether at 0°. Following addition, the mixture was warmed to room temperature and slowly hydrolyzed by dropwise addition of 8.8 ml of H_2O, 8.8 ml of 15% NaOH, and 27 ml of H_2O. The ether extract was filtered, dried (Na_2SO_4), and concentrated and the product was distilled, yield 16.94 g (85%) of **3b**, bp 50–52° (13 mm). Glc analysis of the product on column A showed the product to be >99% pure: ir (neat) 2.98 (OH), 5.95 mμ (C=C); nmr δ 5.45 (t, 1 H, olefinic), 4.13 (d, 2 H, CH_2), 1.95 (s, 1 H, OH), 1.75 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).

Anal. Calcd for $C_5H_{10}O$: C, 69.72; H, 11.70. Found: C, 69.93; H, 11.72.

3-Methyl-2-butenal (3c). A methylene chloride solution of 10.0 g (0.116 mol) of **3b** was added dropwise, over a period of 15 min, to a stirred solution of 110.4 g (1.4 mol) of pyridine and 69.8 g (0.70 mol) of chromic anhydride in 1600 ml of methylene chloride at room temperature. Stirring was continued at room temperature for 2 hr, the mixture was filtered and concentrated, and ether was added to precipitate the salts. The salts were filtered and the process of salt removal was repeated. The solution was extracted twice with 100-ml portions of 5% HCl and then with 100 ml of brine. The ether extract was dried (Na_2SO_4) and concentrated, and the product was distilled, yield 4.7 g (48%) of **3c**, bp

133–135° (760 mm). Glc analysis of the product on column A showed the product to be >99% pure: ir (neat) 6.02 (conjugated C=O), 6.14 mμ (C=C); nmr δ 10.05 (d, 1 H, aldehydic proton), 5.92 (d, 1 H, olefinic), 2.17 (d, 3 H, J = 1 Hz, methyl), 1.98 (d, 3 H, J = 1 Hz, methyl).

2-Bromomethyl-1,3-butadiene (4a). This compound was prepared by the method of Krug and Yen[7] in 18% over-all yield. Glc analysis on column B showed the product to be 90% pure: ir (neat, glc pure) 6.28 (conjugated C=C), 11.05 mμ (olefinic C–H bend); nmr δ 6.42 (dd, 1 H, J = 17.5, 11.0 Hz, olefinic), 5.16–5.66 (m, 4 H, olefinic), 4.12 (s, 2 H, CH_2); mass spectrum m/e 146, 148 (M^+), 41, base peak ($C_3H_5^+$), 67 ($M^+ - Br$).

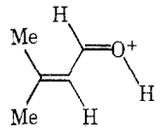
3-Methyl-3,4-oxido-1-butene (5). This epoxide was prepared according to a modification of the procedure of Reist, Junga, and Baker.[8] Isoprene (76.1 g, 1.12 mol) was emulsified by rapid stirring in 250 ml of water and the emulsion was cooled to 0°. *N*-Bromosuccinimide (200 g, 1.12 mol) was added slowly over a period of 0.5 hr and stirred for an additional 3 hr at 0°, and the organic phase was separated, combined with an ether extract of the aqueous phase, and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a yellow oil containing crystals of succinimide which were removed by filtration; yield 160 g (87%) of a mixture of bromohydrins which was not further characterized.

The total bromohydrin product (160 g) was added over a 20-min period to 300 g of a rapidly stirred solution of 30% aqueous sodium hydroxide at 0°, and was stirred for an additional 2 hr at 0°. The organic phase was removed, combined with an ether extract of the aqueous layer, dried ($MgSO_4$), and fractionally distilled. A fraction (32.5 g, 34.5% overall yield) boiling at 78.0–82.1° (lit.[8] bp 79–82°) contained the desired epoxide **5**: nmr (CCl_4) δ 1.35 (s, 3 H), 2.58 (dd, J = 10.0, 6.0 Hz, 2 H), 4.98–5.80 (m, 3 H, olefinic).

2-Hydroxymethyl-1,3-butadiene (4b). Lithium diisopropylamide (18.0 g, 0.168 mol) was dissolved in 300 ml of anhydrous ether, and the epoxide **5** (11.0 g, 0.130 mol) was added over a 10-min period. After reflux had ceased, the solution was cooled to room temperature and poured into 200 ml of 2.0 M HCl. The organic layer was isolated, washed with 5% sodium bicarbonate, and dried ($MgSO_4$). Solvent was removed under vacuum to give 8.3 g (0.099 mol, 76% yield) of the desired alcohol **4b** as a brown oil. This material was used without purification, because its purification is difficult. However, distillation from 0.5 g of hydroquinone gave 3.3 g (0.039 mol, 30% yield) of **4b**, bp 69° (35 mm), as a clear liquid. Glc analysis on column C showed the product to be 99% pure, and its spectroscopic properties (nmr) were identical with those of a sample prepared from 2-bromomethyl-1,3-butadiene (**4a**) by the method of Thomas.[11]

2-Bromomethyl-1,3-butadiene (4a) from 2-Hydroxymethyl-1,3-butadiene (4b). The alcohol **4b** (2.0 g, 0.0238 mol) was dissolved in 50 ml of ether and cooled in an ice–salt bath. Phosphorus tribromide (2.16 g, 0.008 mol) was added dropwise over a 20-min period; the reaction mixture was then stirred in the absence of light at ice–salt temperatures for 30 min and then for 2 hr at 25°. The organic layer was extracted with 100 ml of 5% bicarbonate solution and dried ($MgSO_4$), and the solvent was removed to give 1.5 g (0.0102 mol, 43% yield) of the bromide **4a**. This material was 97% pure by glc analysis (column C) and had the same spectroscopic properties (nmr, ir) as the material prepared by the method of Krug and Yen[7] (see above).

2-Methyl-6-methylene-2,7-octadien-4-ol (1). To 30 ml of dry THF was added 2.43 g (0.037 mol) of zinc (99% pure, dried under vacuum over P_2O_5), 4.16 g (0.026 mol based on 90% purity by glc) of **4a**, and 2.36 g (0.028 mol) of **3c**. Compounds **4a** and **3c** had been dried overnight over molecular sieves. The mixture was refluxed with stirring for 4 hr (oil bath at 68°), cooled to room temperature, and hydrolyzed by addition to a stirred mixture of ether and water. The salts were filtered, and the ether layer was washed once with 25 ml of H_2O and transferred to a flask containing 4A molecular sieves. Salt was added to the combined water layers and this layer was extracted with 50 ml of ether. The ether extracts were combined, dried for 36 hr over 4A molecular sieves, and concentrated, and the remaining traces of solvent were removed in a micro distillation apparatus at room temperature by slowly reducing the pressure from 760 to 2 mm. The remaining oil was warmed to 30° and the pressure was reduced to 0.15 mm. The temperature of the oil bath was slowly increased. The product was collected in an ice-cooled trap, yield 2.57 g (65%) of **1**: bp 54–59° (0.15 mm); ir (CCl_4) 3605 (OH), 3085 (C=C), 901 cm^{-1} (olefinic C–H bend); nmr δ 6.41 (dd, 1 H, J = 18, 9 Hz, olefinic), 5.36–4.90 (m, 5 H, olefinic protons), 4.52 (m, 1 H, methine proton), 1.74 (d, 3 H, J = 1 Hz, CH_3), 1.69 (d, 3 H, J = 1 Hz, CH_3), 1.56 (s, 1 H, OH); mass spectrum m/e 152 (M^+), 85, base peak.



These spectra were identical with those of an authentic sample of **1** obtained from Chemical Samples Co. Glc analysis of a sample of distilled **1** on column B (column temperature 140°, injection temperature 140°) showed the sample to be >95% pure.

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Registry No.—**1**, 14434-41-4; **3a**, 3350-78-5; **3b**, 556-82-1; **3c**, 107-86-8; **4a**, 23691-13-6; **4b**, 13429-21-5; **5**, 1838-94-4; 3-methyl-2-butenoic acid, 541-47-9; isoprene, 78-79-5; *N*-bromosuccinimide, 128-08-5.

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A Practical Synthesis of α-Methylene-γ-butyrolactone

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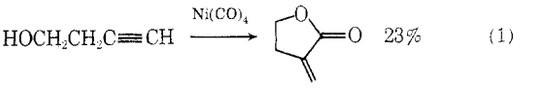
The unsubstituted α-methylene-γ-butyrolactone **1** was isolated by hydrolysis of a glycosidic substance occuring in *Erythronium americanum*.[1] More recently a fungitoxic substance identified as **1** has been isolated from tulips.[2] The structure of **1** has been confirmed by spectral data and synthesis. The primary interest in **1** stems from the presence of the α-methylene-γ-butyrolactone ring system in many natural products of biological interest[3] and the need for new efficient synthetic methods for the introduction of the α-methylene unit from lactone precursors.[4] Previous syntheses of **1** have involved as the key step (a) the reaction of a β,γ-acetylenic carbinol with nickel carbonyl (eq 1),[5] (b) the zinc bromide treatment of ethyl 1-hydroxymethylcyclopropanecarboxylate in hydrobromic acid (eq 2),[6] and (c) the reductive animation of an α-formyl lactone (eq 3).[4f]



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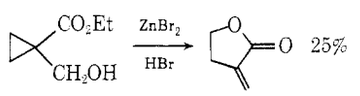

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