Stereospecific Total Synthesis of (±)-Vetiselinenol

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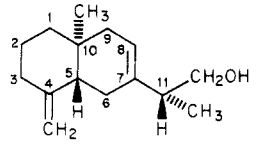
(±)-Vetiselinenol (1) and (±)-11-epivetiselinenol (12) have been synthesized by stereospecific routes using methyl lactones 4 and 3 to establish the desired stereochemistry at C-11. Equilibration studies indicated that the thermodynamic mixture of the lactones 3/4 is 45:55. Reductive opening of the lactones, selective acetylation, dehydration, and hydrolysis gave 1 and 12. Both 1 and 12 were converted to (±)-vetiselinene (15), establishing that they were indeed C-11 epimers.

As part of our interest in synthetic approaches to eudesmane sesquiterpenes[1-3] we undertook an investigation of the synthesis of vetiselinenol[4,5] (1), an antipodal eude-



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smane sesquiterpene isolated from vetiver oils. Of particular interest to us were the Δ^7 double bond and the stereochemistry in the C-7 side chain. We now report a stereospecific total synthesis of the racemic form of this compound as well as its C-11 epimer.

Based on previous work[6] on some tetrahydroalantolactones it was felt that the side-cahin stereochemistry (C-11) could be controlled from an appropriate methyl lactone. The incorporation of the Δ^7 double bond would be facilitated by the presence of an hydroxyl group at C-8.

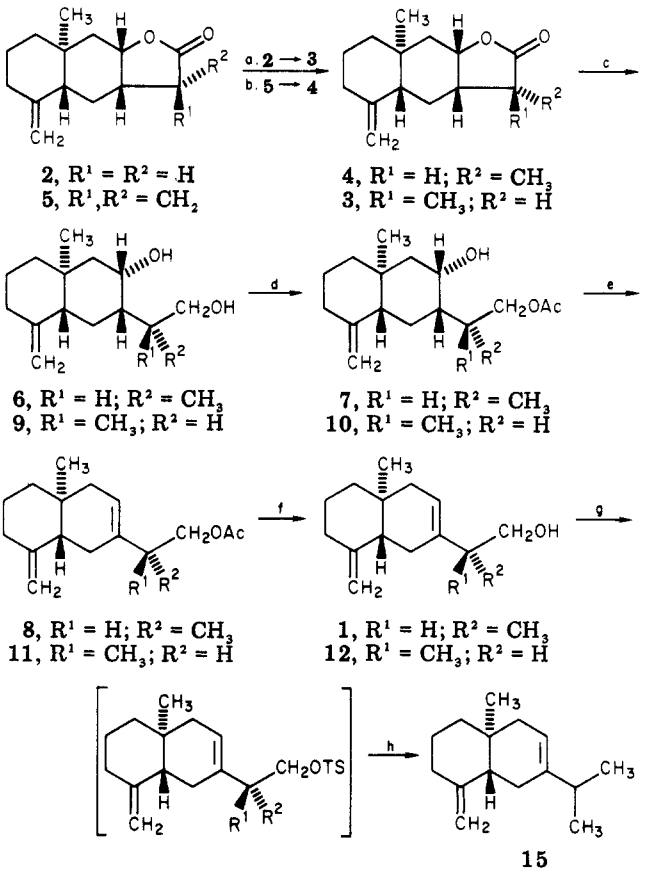
A methyl lactone could be prepared by direct methylation of lactone 2[2] (see Scheme I). A single, crystalline product 3 was obtained in 90% yield. The nuclear magnetic resonance (^{1}H) spectrum of this compound indicated a β-configuration at C-11.[7]

An equilibrium to the thermodynamic mixture of methyl lactones was accomplished by treating lactone 3 with potassium carbonate in hot tetralin, a system thought to leave the lactone in its closed form during equilibration.[6] GLC analysis of the mixture indicated an equilibrium ratio of α-isomer (4)/β-isomer (3) of 55:45. In light of this result, the exclusive formation of the β-isomer 3 from reaction of lactone 2 with lithium diisopropylamide and methyl iodide was a result of kinetic control.

$$3 \underset{\text{tetralin, 180 °C}}{\overset{K_2CO_3}{\rightleftharpoons}} 4$$

Equilibrative systems have been reported for tetrahydroalantolactone[6] which would effect a low-yield conversion of the β-isomer 3 to the α-isomer 4. In our hands these systems met with little success and were abandoned in lieu of a method of stereoselectively introducing the C-11 methyl group directly into the α-configuration.

Scheme I[a]



[a] a, LDA, MeI; b, $NaBH_4$, MeOH; c, $LiAlH_4$, Et_2O; d, Ac_2O, pyr; e, $POCl_3$, pyr; f, KOH, MeOH; g, TsCl, pyr; h, $LiAlH_4$, THF.

Lactone 2 was converted into racemic isoalantolactone (5, using the vetiselinenol absolute stereochemistry) by our previously described route.[2] Reduction of this lactone with sodium borohydride in methanol (see Scheme I) by analogy to the antipodal isolantolactone series[8] produced the desired lactone 4 (racemic dihydroalantolactone) as a white crystalline solid in 88% yield. The nuclear magnetic resonance (^{1}H) spectrum of this compound was in good agreement with that reported for optically active dihydroisoalantolactone.[7,8] Equilibration of methyl lactone 4 with potassium carbonate and hot tetralin gave an equilibrium ratio of 4/3 of 58:42, a value in good agreement

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(7) A doublet of δ 1.25 (J = 7.5 Hz) was observed for the C-11 methyl group. The expected value for an α-orientation is δ 1.17 (J = 7 Hz); see: Marshall, J. A.; Cohen, N. *J. Org. Chem.* **1964**, *29*, 3727.
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with that obtained from equilibration of β-isomer 3.

With the desired stereochemistry established at C-11, introduction of the Δ^7 double bond was the next task (see Scheme I). Reduction of lactone 4 with lithium aluminum hydride produced a diol 6 which, without purification, was reacted with acetic anhydride in pyridine. Careful control of the reaction conditions has given near quantitative yields of the desired monoacetate 7. (Earlier attempts to protect the primary alcohol as a trityl ether were unsuccessful, producing a material apparently containing a tetrahydrofuran moiety.) It had been shown in work[9] on optically active dihydroisoalantolactone that the reduction step maintained the stereochemical integrity at C-11.

Dehydration of monoacetate 7 with phosphorus oxychloride in pyridine produced the desired olefin 8 as the sole product. Without purification, this compound was hydrolyzed with potassium hydroxide in aqueous methanol to yield (±)-vetiselinenol (1), which had superimposable infrared and nuclear magnetic resonance spectra with those of natural vetiselinenol.[10]

An analogous series of reactions (see Scheme I) was employed to convert methyl lactone 3 into (±)-11-epivetiselinenol (12). This latter compound gave very similar nuclear magnetic resonance spectra to that of (±)-vetiselinenol in the solvents carbon tetrachloride and deuteriochloroform but was differentiated from (±)-vetiselinenol in benzene-d_6.

Finally, to demonstrate that the sole difference between synthetic (±)-vetiselinenol (1) and (±)-11-epivetiselinenol (12) was the stereochemistry at C-11, we converted these two compounds to (±)-vetiselinene (15), a derivative containing no side-chain asymmetry. In an analogous route to the one Andersen[4] used to convert natural vetiselinenol to vetiselinene, compounds 1 and 12 were converted to their tosylate derivatives with *p*-toluenesulfonyl chloride in pyridine. The crude tosylates (13 and 14) were reduced with lithium aluminum hydride to give a mixture of the starting alcohol (1 or 12) and (±)-vetiselinene (15). Chromatography yielded hydrocarbons from both series which were identical with each other and had superimposable infrared and nuclear magnetic resonance spectra with those of natural vetiselinene.[10]

Experimental Section

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Beckman IR-8 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-360 instrument. Chemical shifts are quoted in parts per million downfield from internal tetramethylsilane. High-resolution mass spectra were obtained with a Varian M-66 spectrometer. Combustion analysis were done by Chemalytics, Inc., Tempe, AZ. Petroleum ether was reagent grade with boiling range 30–60 °C. All reactions were carried out under a N_2 atmosphere. Anhydrous Na_2SO_4 was used as the drying agent. Florisil (60/100 A) used for chromatography was purchased from Wilshire Chemical Co., Inc.

Methyl Lactone 3. To a flask containing a solution, precooled in a dry ice–acetone bath, of lactone 2[2] (514 mg, 2.34 mmol) in tetrahydrofuran (20 mL) was added a solution of lithium diisopropylamide [made from diisopropylamine (1.06 g, 10.5 mmol) and *n*-butyllithium (5.03 mL of 1.49 M solution, 7.49 mmol)] in tetrahydrofuran (30 mL). The mixture was stirred for 15 min and methyl iodide (2.99 g, 21.1 mmol) was rapidly added. The resulting solution was allowed to warm to room temperature and then was poured into ether. This mixture was washed with 3 N hydrochloric acid, water, sodium bicarbonate solution, and brine and dried. After solvent removal and Florisil chromatography (elution with 40:60 CH_2Cl_2–C_5H_{12}), methyl lactone 3 was obtained as a crystalline solid (492 mg, 2.10 mmol, 90% yield). Recrystallization from an ether–petroleum ether mixture gave needles: mp 124–125 °C; IR (KBr) 1750 (C=O), 1640 (C=C), 890 cm^{-1} (>C=CH_2); NMR (CCl_4) δ 0.87 (s, 3 H), 1.26 (d, J = 7 Hz, 3 H), 4.50 (br s, 1 H), 4.63 (m, 1 H), 4.78 (br s, 1 H). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.80; H, 9.52.

Equilibration of Lactone 3. A mixture of lactone 3 (20 mg), potassium carbonate (100 mg), and tetralin (3 mL) was stirred at 180 °C. After 12 days the mixture was cooled, poured into water, and extracted with ether. The ether layers were combined, washed with water and brine, dried, and concentrated. The mixture of lactones was eluted from a Florisil column (40:60 CH_2Cl_2–petroleum ether). GLC analysis (35-m SE-30 glass capillary column) indicated a 45:55 ratio of lactone 3 to lactone 4.

Methyl Lactone 4. To a cooled (0 °C) solution of (±)-isoalantolactone[2] (702 mg, 3.02 mmol) in methanol (50 mL) was added sodium borohydride (702 mg, 18.5 mmol). The mixture was stirred for 30 min, allowed to warm to room temperature, poured into water (50 mL), and extracted with methylene chloride. The methylene chloride layers were combined, extracted with water, dried, and concentrated to give crystalline lactone 4 (621 mg, 2.65 mmol, 88% yield). Recrystallization from ether–petroleum ether gave needles: mp 137.5–139 °C; IR (KBr) 1750 (C=O), 1635 (C=C), 882 cm^{-1} (>C=CH_2); NMR (CCl_4) δ 0.82 (s, 3 H), 1.16 (d, J = 7 Hz, 3 H), 1.0–3.0 (m, 12 H), 4.37 (m, 1 H), 4.48 (br s, 1 H), 4.75 (br s, 1 H). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.96; H, 9.80.

Equilibration of Lactone 4. A mixture of lactone 4 (21 mg), potassium carbonate (100 mg), and tetralin (5 mL) was stirred at 180 °C for 8 days. Workup and analysis as for the equilibration of lactone 3 indicated a 42:58 ratio of lactone 3 to lactone 4.

Monoacetate 7. To a solution of 0.91 M lithium aluminum hydride in tetrahydrofuran (4.37 mL, 3.97 mmol) and ether (50 mL) was added lactone 4 (621 mg, 2.65 mmol) in ether (20 mL). This mixture was stirred for 1 h at room temperature. Water (0.151 mL) was added followed after 5 min by 15% sodium hydroxide solution (0.453 mL). The resulting heterogeneous mixture was stirred for 5 min and finally more water (0.151 mL) was added. The resulting precipitate was filtered; the filtrate was dried and concentrated to give crude diol 6 (761 mg). This material was used without further purification.

To the crude diol 6 (761 mg) was added a solution of acetic anhydride (405 mg, 3.97 mmol) in pyridine (24 mL). The mixture was stirred for 45 h at room temperature, then poured into water, and extracted with ether. The ether extracts were washed with 3 N hydrochloric acid, 3 N sodium hydroxide, water, and brine, dried, and concentrated to give 833 mg of crude material. Elution from Florisil (75:25 CH_2Cl_2–petroleum ether) gave oily monoacetate 7 (732 mg, 2.61 mmol, 99% yield): IR (neat) 3520 (OH), 1718 (C=O), 1640 (C=C), 1244 (C—O), 885 cm^{-1} (>C=CH_2); NMR (CCl_4) δ 0.93 (s, 3 H), 1.00 (d, J = 6 Hz, 3 H), 2.00 (s, 3 H), 4.00 (m, 3 H), 4.47 (br s, 1 H), 4.68 (br s, 1 H); high-resolution mass spectrum, m/e calcd for $C_{17}H_{26}O_2$ (M – H_2O) 262.1933, found 262.1953.

In other experiments, further elution of the Florisil column [3:97 Et_2O–CH_2Cl_2] gave the crystalline diol 6. Recrystallization from ether–petroleum ether produced white crystals: mp 107–108 °C; IR (KBr) 3205 (OH), 1640 (C=C), 885 cm^{-1} (>C=CH_2); NMR ($CDCl_3$) δ 0.94 (d, J = 7 Hz, 3 H), 0.95 (s, 3 H), 3.47 (m, 2 H), 3.93 (br s, 3 H), 4.52 (br s, 1 H), 4.72 (br s, 1 H). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.09; H, 11.05.

(±)-Vetiselinenol (1). To a solution of monoacetate 7 (732 mg, 2.61 mmol) in anhydrous pyridine (100 mL) was added phosphorous oxychloride (5 mL, 54.6 mmol). After being stirred at room temperature for 16 h the reaction mixture was cooled to 0 °C and ice was added. The mixture was poured into ether and washed with 20% sodium hydroxide, water, 3 N hydrochloric acid, water, and brine, dried, and concentrated to give a quantitative yield (698 mg) of crude oily acetate 8. This material was used without further purification although in other experiments Florisil chromatography (elution with 20:80 CH_2Cl_2–C_5H_{12}) gave pure material: IR (neat) 1740 (C=O), 1638 (C=C), 1232 (C—O), 885 cm^{-1} (>C=CH_2); NMR (CCl_4) δ 0.68 (s, 3 H), 1.02 (d, J = 7 Hz, 3 H), 1.90 (m, 4 H), 1.95 (s, 3 H), 3.93 (d, J = 7 Hz, 2 H), 4.52 (br s, 1 H), 4.73 (br s, 1 H), 5.33 (br s, 1 H).

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(10) We thank Professor Niels H. Andersen, University of Washington, for a sample of this compound.

To the crude elimination product obtained above was added 50 mL of 5% potassium hydroxide in methanol. After being stirred for 16 h at room temperature, the mixture was poured into water and extracted with methylene chloride. The combined methylene chloride layers were washed with water and brine, dried, and concentrated. Elution from Florisil (50:50 CH_2Cl–C_5H_{12}) gave oily (±)-vetiselinenol (557 mg, 2.53 mmol, 97% yield), identical in all respects with the IR and NMR spectra of a sample of natural (-)-vetiselinenol:[10] IR (neat) 3360 (OH), 1640 (C=C), 890 cm^{-1} (>C=CH_2); NMR (C_6D_6) δ 0.73 (s, 3 H), 1.01 (d, J = 6 Hz, 3 H), 1.93 (s, 4 H), 1.0–2.6 (complex, 9 H), 3.48 (m, 2 H), 4.67 (br s, 1 H), 4.88 (br s, 1 H), 5.37 (br s, 1 H); high-resolution mass spectrum, m/e calcd for $C_{14}H_{21}O$ (M - CH_3) 205.1592, found 205.1618.

Monoacetate 10. In a manner analogous to the preparation of monoacetate **7**, methyl lactone **3** (383 mg, 1.64 mmol) was reduced with lithium aluminum hydride to give 385 mg of crude diol **9**. This material was acetylated without further purification.

The acetylation was carried out as before except that the reaction time was 21 h. Elution of the crude product (497 mg) from Florisil (75:25 CH_2Cl_2–C_5H_{12}) gave oily monoacetate **10** (251 mg, 0.896 mmol, 55% conversion, 79% yield based on recovered diol **9**): IR (neat) 3495 (OH), 1725 (C=O), 1642 (C=C), 1245 (C—O), 885 cm^{-1} (>C=CH_2); NMR (CCl_4) δ 0.92 (s, 3 H), 1.02 (d, J = 6 Hz, 3 H), 2.02 (s, 3 H), 4.00 (m, 3 H), 4.47 (br s, 1 H), 4.68 (br s, 1 H); high-resolution mass spectrum, m/e calcd for $C_{17}H_{26}O_2$ (M - H_2O) 262.1933, found 262.1920.

Further elution of the Florisil column (3:97 Et_2O–CH_2Cl_2) gave crystalline diol **9** (115 mg, 0.483 mmol). Recrystallization from ether–petroleum ether produced white crystals: mp 113.5–114 °C; IR (KBr) 3175 (OH), 1635 (C=C), 885 cm^{-1} (>C=CH_2); NMR (CCl_4) δ 0.93 (s, 3 H), 0.98 (d, J = 6 Hz, 3 H), 3.55 (br s, 2 H), 4.10 (br s, 1 H), 4.47 (br s, 1 H), 4.67 (br s, 1 H). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.40; H, 10.84.

(±)-11-Epivetiselinenol (12). In a manner analogous to the preparation of (±)-vetiselinenol from monoacetate **7**, monoacetate **10** (180 mg) was dehydrated to give a quantitative yield (168 mg) of oily acetate **11** after Florisil chromatography (elution with 10:90 CH_2Cl_2–C_5H_{12}): IR (neat) 1738 (C=O), 1638 (C=C), 1230 (C—O), 886 cm^{-1} (>C=CH_2); NMR (CCl_4) δ 0.68 (s, 3 H), 1.04 (d, J = 7 Hz, 3 H), 1.92 (m, 4 H), 1.95 (s, 3 H), 3.93 (dd, J = 7, 3 Hz, 2 H), 4.53 (br s, 1 H), 4.75 (br s, 1 H), 5.35 (m, 1 H).

The elimination product above was hydrolyzed as before to give (±)-11-epivetiselinenol (140 mg, 0.64 mmol, 100% yield) after Florisil chromatography (elution with 50:50 CH_2Cl_2–C_5H_{12}): IR (neat) 3360 (OH), 1638 (C=C), 887 cm^{-1} (>C=CH_2); NMR (C_6D_6) δ 0.70 (s, 3 H), 0.94 (d, J = 7 Hz, 3 H), 1.90 (s, 4 H), 1.0–2.6 (complex, 9 H), 3.42 (d, J = 7 Hz, 2 H), 4.65 (br s, 1 H), 4.88 (br s, 1 H), 5.37 (m, 1 H); high-resolution mass spectrum, m/e calcd for $C_{14}H_{21}O$ (M - CH_3) 205.1592, found 205.1598.

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Registry No. (±)-**1**, 72257-40-0; (±)-**2**, 54911-04-5; (±)-**3**, 77480-20-7; (±)-**4**, 77480-21-8; (±)-**5**, 4677-48-9; (±)-**6**, 77480-22-9; (±)-**7**, 77415-51-1; (±)-**8**, 77429-54-0; (±)-**9**, 77480-23-0; (±)-**10**, 77480-24-1; (±)-**11**, 77415-52-2; (±)-**12**, 77480-25-2.

Notes

Methanesulfonic Acid Catalyzed Cyclization of 3-Arylpropanoic and 4-Arylbutanoic Acids to 1-Indanones and 1-Tetralones

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Several acidic reagents are available for the preparation of cyclic ketones from 3- and 4-aryl-substituted carboxylic acids.[1] Literature references to the use of methanesulfonic acid (MSA) for this purpose are meager.[2] Eaton and Carlson[3] describe a cyclization procedure using a hot mixture of MSA and P_2O_5. Since MSA ordinarily does not cause sulfonation of aromatic rings, we considered that neat MSA, at elevated temperatures, should be a superior cyclizing reagent because of its acidity and excellent solvent properties. Table I lists the ketones which have been prepared in this study through cyclization of the appropriate carboxylic acid with hot MSA. The performance of neat anhydrous MSA exceeded our expectations and, in some respects, we believe MSA to be superior to hot PPA as a cyclizing agent. It is more convenient to use and requires about the same reaction time and temperature so that these reagents are potentially interchangeable for cyclization. Color changes from yellow to brown to black during the course of the reaction appear to be indicative of the progress of cyclization as was observed by Koo[4] for PPA cyclization reactions. Our studies under a variety of temperatures, concentrations, and reaction times show that 30 min to 3 h is needed for cyclization, depending on the reactivity of the starting material. We noted that 3-arylpropanoic acids generally require about 20 °C higher reaction temperature (110–115 °C) for the same time needed to cyclize 4-arylbutanoic acids at 90–95 °C. We used preheated MSA to better reproduce the reaction time but see no reason why the reaction cannot be started from laboratory temperature. Concentration studies using 3-phenylpropanoic acid showed that yields improved with dilution up to 7 mL of MSA/g of carboxylic acid. Further dilution did not provide a yield increase. We recommend that anhydrous MSA be used and that moisture be excluded during storage and use.

The use of neat MSA as a substitute for Friedel–Crafts catalyst in intermolecular condensation[9] is not promising.

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(9) This study was carried out at the suggestion of a referee.

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