

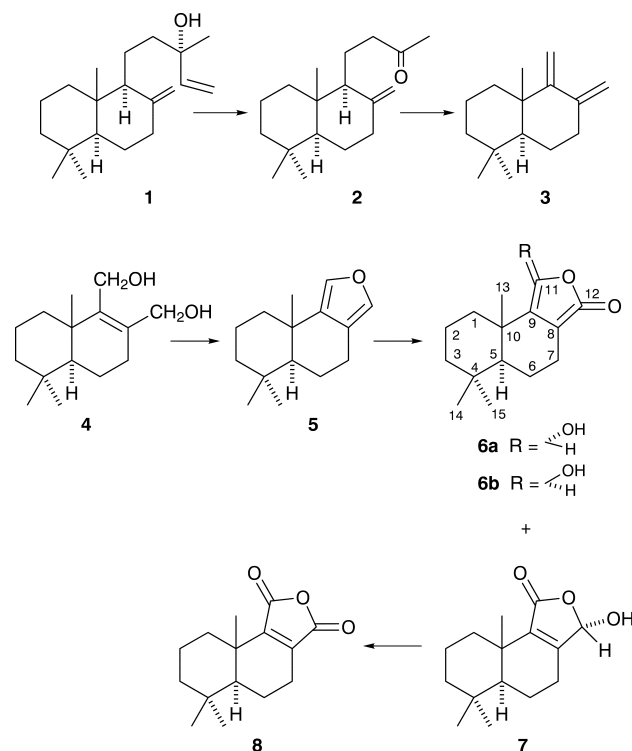
Synthesis of Drimanic Sesquiterpenes, (+)-Valdiviolide, (+)-12 α -Hydroxyisodrimenin and (+)-Winterin†

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The synthesis of (+)-valdiviolide **6a**, (+)-12 α -hydroxyisodrimenin **7** and (+)-winterin **8**, from manool **1** is described.

The biologically active drimane-type sesquiterpenes have been a target for organic synthesis in various laboratories over the past ten years. In recent years we have developed a new highly efficient method for the synthesis of optically active, drimane-related natural products. The key reaction consists of the oxidation of commercially available manool **1** and the Norrish type II cleavage of the resulting ketone **2** to the diene **3** (52% overall yield), which can be utilised as a common precursor. The sesquiterpenes which have been synthesized so far by employing the diene **3** as a building block include (+)-confertifolin, (+)-isodrimenin, (+)-euryfuran, (–)-warburganal,¹ (+)-albicanol and (+)-bicyclofarnesol.² This paper aims to demonstrate further utility of the diene **3** for the synthesis of (+)-valdiviolide **6a**, (+)-12 α -hydroxyisodrimenin **7** and (+)-winterin **8**.³

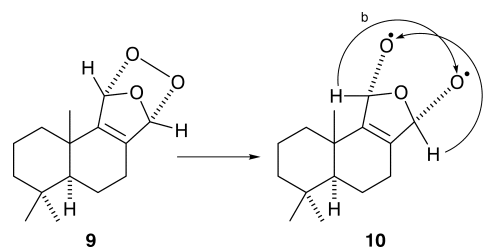


The olefinic 1,4-diol **4**,⁴ prepared from manool **1**, was oxidised with pyridinium chlorochromate to (+)-euryfuran **5** (89%) according to the method reported earlier.⁵ Photooxygenation of the furan **5** in *tert*-butyl alcohol–2,6-lutidine in the presence of eosin⁶ afforded a 2:1 mixture of two isomeric products. The one which formed in larger amounts

(50%) was found to be identical with (+)-valdiviolide **6a** according to reported spectroscopic data.^{6,7} The α stereochemistry of the 11-OH group of this compound was confirmed by the NOE experiment. Irradiation at the signal (δ 1.23) of the C-13 methyl group resulted in enhancement (20%) of the signal of the proton (δ 6.04) at C-11. This indicates that the 11-proton possesses the β configuration and hence the 11-OH group is α -oriented.

Previously Ley and Mahon⁶ reported that photooxygenation of the furan **5** under the same conditions afforded two products. The major product was identical with valdiviolide **6a**, but they assigned the other minor product the structure **6b** (11-epivaldiviolide) without reporting spectroscopic evidence.

We have analysed carefully the structure of this minor product, obtained in 25% yield, by means of 2D-NMR ¹H and ¹³C single bond and multiple bond correlation studies. The carbonyl carbon resonance appeared at δ 170.35. The two olefinic carbons resonated at δ 138.48 and 168.18. The resonance (δ 168.19) at lower field correlated through two bonds to the proton (δ 5.83) bearing the hydroxy group. The resonance (δ 138.48) at higher field was assignable to the carbon located α to the carbonyl group and this olefinic carbon showed three-bond correlation to the protons (δ 1.10) of the C-13 methyl group. This verified that the carbonyl group should be situated at C-11. Therefore, we formulated this compound as **7**. The formation of compound **7** and the stereochemistry of its 12-OH group was deduced from the reaction mechanism of the photooxygenation. As illustrated in Scheme 1, the attack of the oxygen from the less sterically hindered α side would afford the intermediate α -endo-peroxide **9**. Subsequent breakdown of the peroxide would form the biradical species **10**, which would then terminate by disproportionation in two ways. Transfer of the C-12 hydrogen to the C-11 oxygen radical (see arrow a) would lead to compound **6a**, while transfer of the C-11 hydrogen to the C-12 oxygen radical (see arrow b) would afford compound **7**.



Scheme 1

It should be noted that compound **7**, that is 12 α -hydroxyisodrimenin has recently been isolated as a mixture of epimers at the hemiacetal carbon from sponge *Dysidea fusca*.⁸ Oxidation of compound **7** with the Jones reagent⁹ afforded compound **8** (60%) identical with (+)-winterin.⁷

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Experimental

Mps were measured with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded with a Bruker AM-300 spectrometer for solutions in CDCl₃, mass spectra with a Kratos MS25RFA at 70 eV using a direct inlet system. Rotations were measured at 23 °C with a Zeiss "0.01" polarimeter. Merck silica gel (70–230 mesh ASTM) was used for column chromatography. TLC was performed on Merck silica gel 60 G₂₅₄ and the spots were observed either by exposure to iodine vapour or by UV light. All organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure below 60 °C.

Photo-oxygenation of the Furan 5.—A solution of the furan **5** (80 mg, 0.36 mmol) in *tert*-butyl alcohol–2,6-lutidine (27 ml, 2:1) containing eosin (2.6 mg) was irradiated at 15 °C with an external 150 W tungsten lamp for 6 h during which time oxygen was bubbled through the reaction mixture. The solvent was evaporated under reduced pressure and the residue chromatographed over silica gel. Elution with 30% diethyl ether in hexane afforded a 2:1 mixture of compounds **6a** and **7**, as an oil, as evidenced by the ¹H NMR spectrum. Crystallisation from hexane gave pure compound **6a**, mp 172–175 °C (44 mg, 50% yield); [α]_D+107° (*c* 1.7, CHCl₃); *m/z* 250 (M⁺); δ_{H} (300 MHz) 0.89 (3 H, s, 14-Me), 0.90 (3 H, s, 15-Me), 1.23 (3 H, s, 13-Me), 4.00 (1 H, OH-11) and 6.04 (1 H, m, H-11); δ_{C} (75.45 MHz) 35.27 (C-1), 17.89 (C-2), 41.69 (C-3), 33.44 (C-4), 51.51 (C-5), 18.28 (C-6), 21.19 (C-7), 127.63 (C-8), 168.49 (C-9), 36.82 (C-10), 97.51 (C-11), 172.18 (C-12), 19.60 (C-13), 21.59 (C-14) and 33.35 (C-15).

Chromatography of the mother-liquor of compound **6a** over silica gel with hexane–ether afforded pure compound **7** as an oil; [α]_D+32° (*c* 1.8, CHCl₃); *m/z* 250 (M⁺); δ_{H} (300 MHz) 0.85 (3 H, s, Me), 0.90 (3 H, s, Me), 1.10 (3 H, s, 13-Me) and 5.83 (1 H, s, H-12); δ_{C} (75.45 MHz) 34.90 (C-1), 17.81 (C-2), 41.68 (C-3), 34.18 (C-4), 52.08 (C-5), 18.33 (C-6), 24.13 (C-7), 168.18 (C-8), 138.48 (C-9), 34.66 (C-10), 170.35 (C-11), 96.84 (C-12), 20.15 (C-13), 21.47 (C-14) and 33.43 (C-15) (Found: C, 71.63; H, 8.55. C₁₅H₂₂O₃ requires C, 71.97; H, 8.86%).

Oxidation of Compound 7.—The Jones's reagent was added dropwise to a solution of compound **7** (38 mg) in acetone (3 ml) at room temperature during 15 min. After decomposing the excess of reagent

with methanol, water was added and the product extracted with ether. Evaporation of the ether yielded a residue (34 mg) which was chromatographed over silica gel. Elution with 1% ether in hexane afforded compound **8**, mp 152–153 °C (11 mg, 60%); [α]_D+100° (*c* 0.3, CHCl₃); *m/z* 248 (M⁺); δ_{H} (300 MHz) 0.89 (3 H, s, Me), 0.93 (3 H, s, Me), 1.21 (3 H, s, Me) and 2.3–2.6 (2 H, m, 7-H); δ_{C} (75.45 MHz) 17.62, 18.11, 20.39, 21.36, 22.42, 33.27, 33.29, 34.47, 38.48, 41.39, 51.56, 143.22 (C-8 or C-9), 153.49 (C-9 or C-8), 163.24 (C-11 or C-12) and 164.84 (C-12 or C-11). Further elution with 20% ether in hexane afforded starting material (15 mg).

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