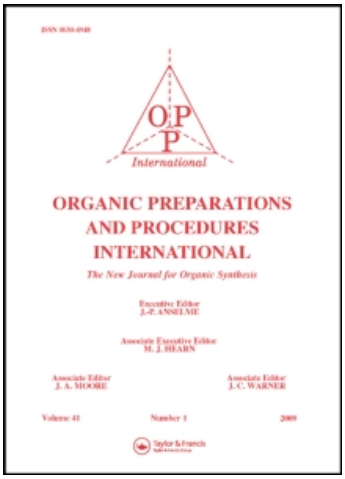

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IMPROVED SYNTHESIS OF 11-ACETOXY-8α-DRIMANOL

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OPPI BRIEFS

IMPROVED SYNTHESIS OF 11-ACETOXY-8α-DRIMANOL

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(10/18/07)

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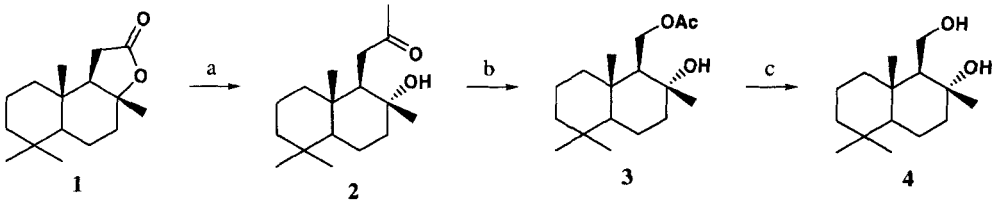
8α,11-Drimanediol (**4**) is a valuable intermediate in the preparation of biologically active, naturally occurring drimanic sesquiterpenes[1-5] and other marine natural products.[6] The most widely referenced method for the preparation of **4** proceeds in three steps from (+)-sclareolide (**1**) (*Scheme 1*).[7]



a) MeLi, Et_2O, room temperature; b) 50% H_2O_2, $(CF_3CO)_2O$, $NaHCO_3$, CH_2Cl_2;
c) KOH, MeOH, room temperature.

Scheme 1

The key step, the Baeyer-Villiger oxidation of ketone **2**, requires an excess of trifluoroperacetic acid, prepared *in situ* from trifluoroacetic anhydride and 50% hydrogen peroxide. The reaction must be buffered by the addition of solid sodium hydrogen carbonate which inhibits undesired acid-catalyzed side reactions (dehydration and/or ketal formation). The yield and quality of the 11-acetoxy-8α-drimanol (**3**) produced by this method is sensitive to the ratio of sodium hydrogencarbonate and trifluoroacetic anhydride used. If the ratio is either greater than, or less than 1:1, the yield of **3** drops dramatically due to the formation of the dehydration products of **2**, and the formation of 12-hydroperoxy-8α,12-epoxy-11-homodrimane.[7] More recently, a communication by Grieco and Hunt[8] described the conversion of **2** using recrystallized MCPBA (1.4 eq) in refluxing dichloromethane over 24 hours, followed by saponification, to give **4** in 70% yield in an approximate 200 mg scale reaction.

Due in part to the necessity to precisely buffer the pertrifluoroacetic acid reaction mixture to ensure a good yield of **3**,[7] but mainly due to our desire to prepare larger quantities of **3**

(20 + gram scale reactions) safely and in a reproducible manner,[9] we have devised the following uncomplicated Baeyer-Villiger oxidation of **2** using permaleic acid.[10] Permaleic acid is prepared *in situ* by the reaction of maleic anhydride with peracetic acid. The peracetic acid is in turn prepared *in situ* from acetic anhydride and 30% hydrogen peroxide. A solution of **2** (20-30 grams) in dichloromethane is added to the solution of permaleic acid and the mixture is stirred at room temperature for 22 hours. The pure ester **3** is isolated in 75% yield after a simple extractive workup followed by silica gel column chromatography. While the method of Grieco and Hunt[8] is an attractive route for the preparation of **4**,[11] our goal was to prepare **3** as safely as possible. Our method, which utilizes the *in situ* generated permaleic acid, allows the Baeyer-Villiger reaction to be performed at room temperature, which in our opinion is a sufficiently safer process, especially on a greater than 20 gram scale.

In conclusion, an efficient and uncomplicated synthesis of 11-acetoxy-8α-drimanol (**3**) has been developed. The method does not require the use of buffer, and is readily scaled-up, providing a much simpler, safer, and less costly alternative to the previously published procedures.[4,7,8]

EXPERIMENTAL SECTION

NMR spectra were recorded in $CDCl_3$ at 500 MHz for ^1H NMR and 150.9 MHz for ^{13}C NMR, using the solvent signal as reference. δ values are given in ppm, coupling constants are given in Hz. The IR spectra were acquired using an FT-IR instrument (KBr pellet). Elemental analysis was performed by Atlantic Microlabs, Norcross, GA, USA. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Mass spectra were obtained by electrospray techniques. All reagents and solvents were purchased from commercial sources and were used without further purification. Chromatographic separations were performed using EM Silica gel 60 (70-230 mesh). Thin-layer chromatography was performed on Merck 60 F_{254} silica gel glass plates.

11-Acetoxy-8α-drimanol (3).- To a cold (5°C), stirred solution of acetic anhydride (100 mL, 1.06 mol) in dichloromethane (130 mL) was added 30% aq. hydrogen peroxide (80.0 mL, 0.783 mol). The reaction mixture was stirred at 5°C for 1 h, and then maleic anhydride (59.6 g, 0.600 mol) was added portionwise at 7-8°C over 0.5 h. The reaction mixture was stirred at 7-8°C for 1 h, and then, warmed to room temperature. A mild exotherm (40°C) was observed and the reaction mixture was then stirred at room temperature for 1.5 h. A solution of 8α-hydroxy-12-oxo-11-homodrimane (**2**)[7] (22.0 g, 0.083 mol) in dichloromethane (70.0 mL) was added dropwise at room temperature over 20 min. After the addition was completed, the reaction mixture was stirred at room temperature for 22 h. Thin-layer chromatography (silica gel, 3:1 hexanes/EtOAc) showed that **2** was consumed. The reaction mixture was diluted with dichloromethane (2 L) and washed with H_2O (2 x 1 L), sat. aq. $NaHCO_3$ (2 x 1 L), and brine (1 L). The organic layer was dried over Na_2SO_4 and evaporated to give a colorless oil (25.5 g). The oil was purified by silica gel column chromatography (1 kg silica gel, 7.5 x 52 cm) eluted with 3:1 hexanes/EtOAc to give

3 (17.65 g, 75%), as a white solid. m.p. 74-77°C (*lit.*[6] 76-78°C).

IR (KBr): 3495, 2922, 1706, 1466, 1263, 1026 cm^{-1}.

^1H NMR ($CDCl_3$): δ 4.37-4.23 (dddd, J = 4.4, 5.3, 11.8, 11.8 Hz, 2H), 2.34 (s, 1H, D_2O exchangeable), 2.04 (s, 3H), 1.91-1.87 (dt, J = 3.2, 12.7 Hz, 1H), 1.68-1.63 (m, 2H), 1.62-1.58 (dt, J = 3.5, 13.7 Hz, 1H), 1.53-1.51 (t, J = 4.8 Hz, 1H), 1.48-1.43 (m, 2H), 1.42-1.38 (m, 1H), 1.31-1.22 (dddd, J = 3.2, 3.3, 13.6, 13.6 Hz, 1H), 1.19-1.13 (dt, J = 3.9, 13.4 Hz, 1H), 1.18 (s, 3H), 1.08-1.02 (dt, J = 3.9, 13.0 Hz, 1H), 0.97-0.94 (dd, J = 2.1, 12.2 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H), 0.81 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 171.4, 72.7, 62.7, 60.1, 55.8, 44.1, 41.9, 39.8, 38.2, 33.6, 33.3, 24.7, 21.7, 21.4, 20.4, 18.5, 15.9.

MS (ES^+): 305 (100%)$(M + Na)^+$, 587 (78%)$(2M + Na)^+$.

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.70. Found: C, 72.50; H, 10.63.

Thin-layer chromatography: silica gel, hexanes/EtOAc (3:1), R_f = 0.19.

The spectral data agreed with those previously published.[4,7]

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9. Attempts to oxidize **2** using sodium hydrogen carbonate buffered trifluoroperacetic acid, prepared from trifluoroacetic anhydride and 30% aq. hydrogen peroxide, failed to give **3**.

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11. The saponification of **3** routinely gives a 95+% yield of **4**. Our overall yield to convert **2** to **4** is 71%, essentially identical to the yield reported by Grieco and Hunt.[8]

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AN IMPROVED SYNTHESIS OF ETHYL 5-CHLORO-4-FLUORO-1*H*-INDOLE-2-CARBOXYLATE

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Indolyl arylsulfones (IASs) are potent non-nucleoside inhibitors of HIV-1 reverse transcriptase (RT).[1] Compound **1** bearing the 5-chloro-4-fluoro substitution pattern at the indole ring, was exceptionally potent against RT WT and RTs carrying drug-resistant mutations. We selected **1** as a lead compound for the development of new second-generation analogues (*Fig 1*).[2]

In 2002, we described a procedure for the synthesis of ethyl 5-chloro-4-fluoro-1*H*-indole-2-carboxylate (**2**) and ethyl 5-chloro-6-fluoro-1*H*-indole-2-carboxylate (**3**)[3] through compound **5** obtained by *N*-chlorosuccinimide chlorination of the ethyl pyruvate 3-fluorophenylhydrazone (**4**) prepared from 3-fluoroaniline *via* the Japp-Klingemann[4] procedure. Fischer[5] cyclization of **5** in the presence of polyphosphoric acid (PPA) as a catalyst, gave the indole esters **2** and **3** which could be separated by repeated chromatography columns (*Scheme 1*). However, since compound **2** was obtained as minor isomer by this procedure,[2] we investigated a more convenient synthesis. We could not find literature describing the synthesis of 4,5-dihalodisubstituted indole-2-carboxylate as the sole isomer, we designed a new synthesis of **2** starting from commercially available 3-fluoro-2-methylaniline (**6**).

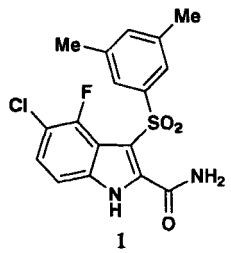

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Fig. 1