Convenient synthesis of drimenol and its oxidation with selenium dioxide

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A convenient synthesis of drimenol by treatment of readily available drimane-8α,11-diol 11-monoacetate with sulfuric acid in ethanol under mild conditions was developed. Oxidation of drimenol with selenium dioxide gives known drim-7-ene-9α,11-diol and drim-7-ene-11,12-diol as the major products.

Key words: terpenoids, drimenol, drimane-8α,11-diol 11-monoacetate, drim-7-ene-9α,11-diol, drim-7-ene-11,12-diol, selenium dioxide, oxidation, dehydration.

Drimenol (**1**) is a very important representative of drimanic sesquiterpenoids. This terpenol has repeatedly served as a starting compound in the synthesis of diverse natural drimanes including those possessing biological activities.[1—4] Drimenol **1** can be isolated from natural sources;[5—7] however, this approach is of little utility, due to the low content of drimenol and the difficulty of its isolation from plants. Therefore, of interest are methods of synthesis of drimenol **1** or its acetate **2** from readily available diterpenoids, especially from bicyclic labdane diterpenoids resembling drimanes most closely in structure.[1,8,9]

This communication describes a simple and an efficient synthesis of drimenol **1** from readily available drimane-8α,11-diol 11-monoacetate (**3**), which we obtained previously[10] in a quantitative yield by peroxide oxidation of 8α-hydroxy-11-bishomodriman-12-one (**4**). In turn, the latter was synthesized in a high yield (65%) from commercially available norambrenolide (**5**),[10] the product of cleavage of many labdane diterpenoids.[11] The oxidation of drimenol with selenium dioxide was studied.

Initially, we attempted to synthesize drimenol **1** by dehydration of monoacetate **3** followed by alkaline hydrolysis of the reaction product (Scheme 1). Of various reagents we tested (oxalyl chloride in DMSO, TsOH in C_6H_6, iodine in C_6H_6, oxalic acid in C_6H_6, $POCl_3$ in pyridine), the reaction of compound **3** with $POCl_3$ in pyridine ensured the highest (80%) product yield. According to GLC data, the reaction affords a mixture of all three possible dehydration products: drimenyl acetate (**2**), albicanyl acetate (**6**), and drim-8-en-11-ol acetate (**7**). Saponification of this mixture with KOH in MeOH gave a mixture of drimenol **1**, albicanol (**8**), and drim-8-en-11-ol (**9**) in 42 : 42 : 16 ratio (^{1}H NMR and GLC data). Unfortunately, we were unable to isolate drimenol (**1**) from this mixture by chromatography on conventional adsorbents. Similar mixtures but with different ratios of products **2**, **6**, and **7** had been prepared previously by dehydration of hydroxyacetate **3** on treatment with $POCl_3$ [8] or $SOCl_2$.[12] Regioselective dehydration of monoacetate **3** to drimenyl acetate (**2**) has also been described;[8] however, the product yield was low (~25%).

Here we propose a simple and an efficient method for the transformation of monoacetate **3** into the desired drimenol **1**. It was found that treatment of monoacetate **3** with an ethanolic solution of H_2SO_4 under mild conditions induces dehydration accompanied by deacetylation to give a crystalline product that was a mixture of drimenol **1** and drim-8(12)-en-11-ol (**8**) in ~10 : 1 ratio formed in a plausible overall yield (~60%). Recrystallization of this mixture from hexane gave pure drimenol **1** (yield 52.8%) whose physicochemical properties coincided with those of an authentic sample prepared by a known procedure.[13]

Having developed an efficient method for the synthesis of drimenol **1**, we further studied its reaction with SeO_2 in order to perform further functionalization of compound **1**. Refluxing of alcohol **1** with SeO_2 in ethanol gives mainly known drim-7-ene-9,11-diol (**10**)[4,14] and drim-7-ene-11,12-diol (**11**)[15—17] (Scheme 2). The physicochemical and spectral characteristics of the resulting compounds fully correspond to published data.[4,14—17]

In addition to diols **10** and **11**, the reaction under these conditions gives also a slight amount of an unknown compound, which was identified as 7α-ethoxydrim-8-en-11-ol (**12**) based on ^{1}H and ^{13}C NMR and IR spectroscopy and mass spectrometry. The width of the signal of the proton at C(7) ($W_{1/2}$ = 5 Hz) in the ^{1}H NMR spec-

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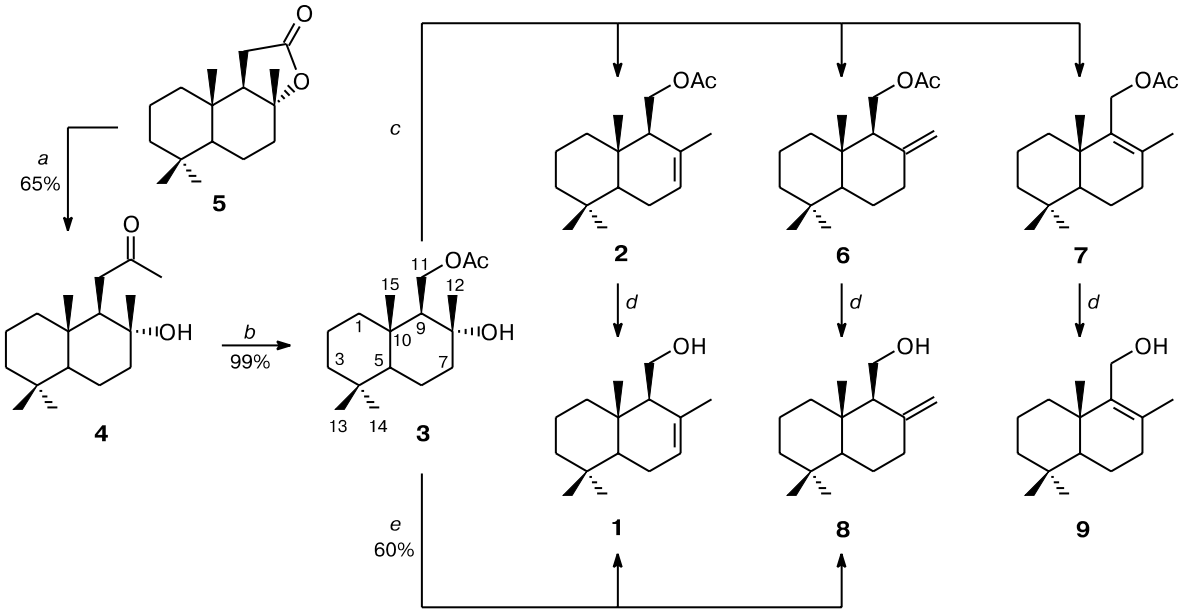
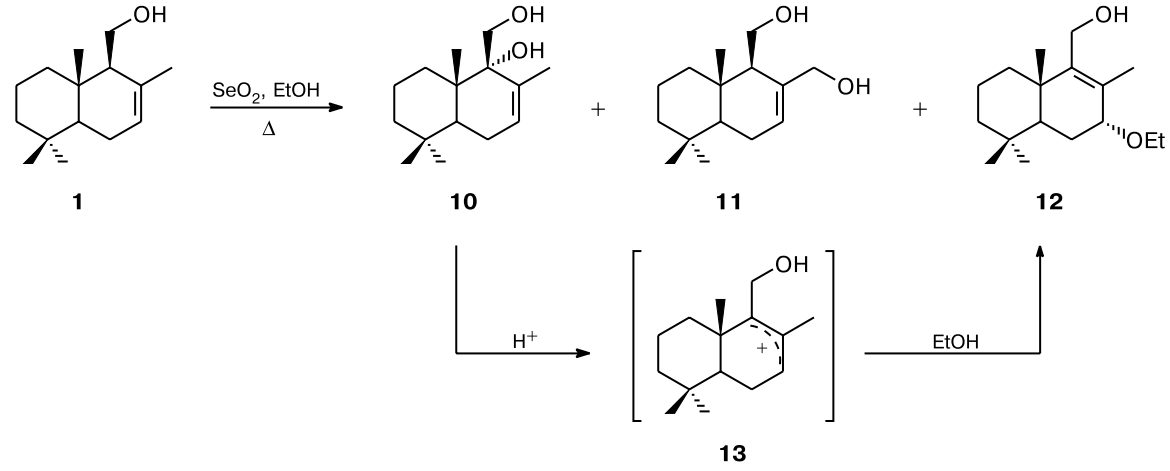
Scheme 1



Reagents and conditions: *a*. CH_3Li, Et_2O, 20 °C, 15 min (see Ref. 10); *b*. 50% H_2O_2, $(CF_3CO)_2O/NaHCO_3$ (1 : 1), CH_2Cl_2, 20 °C, 30 min (see Ref. 10); *c*. $POCl_3$, Py, 20 °C, 2 h; *d*. 10% KOH—MeOH, 20 °C, 20 min, **1** : **8** : **9** = 42 : 42 : 16, total yield on steps *c* + *d* 80%; *e*. 30% H_2SO_4 in EtOH, 20 °C, 18 h; **1** : **8** ~ 10 : 1.

Scheme 2

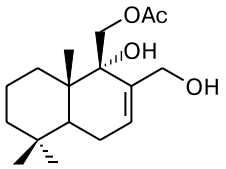


trum of compound **12** indicates that this proton occupies a pseudoequatorial position, while the ethoxy group is in the presudoaxial position. This fact can be attributed to a lower spatial shielding of the α-side in the intermediate carbocation **13** from which the alcohol molecule would attack. The yield of the reaction products **10**, **11**, and **12** depends on the reaction time and, under the optimal conditions (refluxing for 5 h), it amounts to 44, 35, and 8%, respectively.

When drimenol is refluxed with SeO_2 in dioxane for 20 min, a multicomponent mixture of products is formed with diols **10** (yield 35%) and **11** (yield 20%) being the major components. The reaction carried out in acetic acid afforded a complex mixture of products without clearly predominant components, which was not further studied.

It is noteworthy that oxidation of drimenol acetate **2** by refluxing with SeO_2 in dioxane, unlike that of drim-

enol **1**, gives 11-acetoxydrim-7-ene-9α,12-diol (**14**) as the only product (yield 45%),[18] and the reaction with a catalytic amount of SeO_2 in the presence of bis(4-methoxyphenyl) selenoxide as a co-oxidant gives, apart from compound **14** (yield 60%), a smaller amount of 11-acetoxydrim-7-en-12-ol (**15**) (yield 30%)[19].



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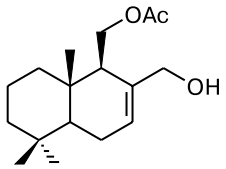

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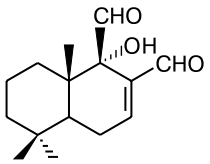

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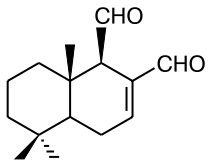

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Thus, we developed a simple and efficient method for the preparation of drimenol **1** and demonstrated that oxidation of compound **1** with SeO_2 gives mainly diols **10** and **11**, which are the known precursors of biologically active drimanes, warburganal **16** and polygodial **17**,[1,4,17,19] and other natural drimanes.[20]

Experimental

Melting points were determined on a Boetius hot stage. IR spectra were recorded on a Specord 74 spectrophotometer in CCl_4. ^1H and ^{13}C NMR spectra were obtained on a Bruker AC-E 200 spectrometer in $CDCl_3$. The chemical shifts are presented in ppm relative to the internal $CHCl_3$ signal (δ 7.24 and 77.00, respectively). The ^{13}C NMR signals were assigned using the DEPT program and by comparison with the spectra of known related compounds.[4,8,15–17] Mass spectra (EI, 70 eV) were recorded on a AEI MS 902 spectrometer. Specific rotation was measured on a JASCO DIP 370 polarimeter in $CHCl_3$. The reactions were monitored by TLC on Silufol plates with visualization by I_2 vapor. GLC analysis was performed on a Chrom-5 chromatograph with a flame ionization detector using a CI-100 A integrator and the following glass columns: (*1*) 5% DC-550 on Chromaton N-AW-DMCS (0.20—0.25 mm), 2500×3 mm, temperature programming from 85 to 225 °C at a rate of 10 °C min^{-1} and (*2*) 10% Carbowax 20 M on Inerton AW-DMCS (0.16—0.20 mm), 1200×3 mm, temperature programming from 90 to 200 °C at a rate of 10 °C min^{-1}; helium was used ad the carrier gas.

Preparation of a mixture of alcohols 1, 8, and 9 from drimane-8α,11-diol 11-monoacetate (3). Phosphorus oxychloride $POCl_3$ (2.25 mL, 3.77 g, 24.58 mmol) was added with stirring over a period of 5 min to an ice-cooled solution of monoacetate **3** (0.6 g, 2.12 mmol)[10] in 11.7 mL of anhydrous pyridine. The reaction mixture was kept for 2 h at ~20 °C and cooled with ice. Cooled 10% aqueous H_2SO_4 was carefully added dropwise with stirring to the reaction mixture. The mixture was extracted with ether (5×30 mL), the extract was washed with 10% H_2SO_4 (10 mL), water (10 mL), a saturated solution of $NaHCO_3$ (2×10 mL), and again with water (2×10 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give 0.54 g (96%) of a mixture of acetates **2**, **6**, and **7** as a colorless liquid. According to GLC (column *1*, identification with addition of authentic compounds[13]), the product ratio was ~46 : 40 : 14. Found (%): C, 77.50; H, 10.54. $C_{17}H_{28}O_2$. Calculated (%): C, 77.22; H, 10.67. IR, ν/cm^{-1}: 1225, 1735 (OAc).

The mixture of products **2**, **6**, and **7** (0.54 g, 2.04 mmol) was dissolved in 10.8 mL of a 10% solution of KOH in MeOH (1.08 g, 19.25 mmol). The solution was kept at room temperature for 20 min, diluted under cooling with 54 mL of water, and extracted with ether (3×50 mL). The extract was washed with water (3×10 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The residue (0.44 g) was chromatographed on a column with 9 g of Acros silica gel (60/200 μm). Elution with a hexane—ether mixture (85 : 15) gave 0.378 g (80%) of a mixture of alcohols **1**, **8**, and **9** in ~42 : 42 : 16 ratio (GLC data, column *2* and ^1H NMR; characteristic signals, δ: 4.70 and 5.00 (both s, $=CH_2$); 5.57 (br.s, C=CH) and 3.89 (m, $C(11)H_2$). The content of compounds **1** and **8** and their sums were determined from the integral curve and the content of the isomer with the tetrasubstituted double bond (**9**) was determined from the difference. Found (%): C, 80.96; H, 11.56. $C_{15}H_{26}O$. Calculated (%): C, 81.02; H, 11.79. ^1H NMR, δ: 0.78 (s, 3 H, $C(15)H_3$); 0.86 (s, 3 H, $C(13)H_3$); 0.93 (s, 3 H, $C(14)H_3$); 1.60 (s, CH_3—C=C); 3.89 (m, 2 H, $C(11)H_2$); 4.70, 5.00 (both s, $C=CH_2$); 5.57 (br.s, C=CH).

Preparation of drimenol 1 from drimane-8α,11-diol 11-monoacetate (3). A solution of monoacetate **3** (2.67 g, 9.45 mmol) in 26.7 mL of a 30% solution of conc. H_2SO_4 in EtOH was left at ~20 °C for 18 h (TLC monitoring). Water (270 mL) was added to the reaction mixture and the mixture was neutralized with dry $NaHCO_3$ and extracted with ether (5×100 mL). The extract was washed with water (50 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The crystalline residue (2.31 g) was recrystallized from hexane to give 1.24 g of a product with m.p. 76—82 °C; according to GLC (column *2*), this product contained 90.6% of drimenol **1** and 9.2% of its isomer **8**. Repeated crystallization from hexane gave 1.11 g (yield 52.8%) of drimenol **1**, m.p. 94—95 °C $[\alpha]_D^{24}$ −17.7 (*c* 2.1, benzene) (*cf.* lit: m.p. 96—96.5 °C, $[\alpha]_D$ −18.36 (benzene)[13]; m.p. 97—98 °C, $[\alpha]_D$ −18.0 (benzene)[21]). IR, ν/cm^{-1}: 827, 1653 (C=CH), 1020, 3380 (br), 3653 (OH). ^1H NMR, δ: 0.87 (s, 6 H, $C(15)H_3$, $C(13)H_3$); 0.89 (s, 3 H, $C(14)H_3$); 1.80 (s, 3 H, $C(12)H_3$); 3.81 (m, 2 H, $C(11)H_2$); 5.53 (m, 1 H, C(7)H).

Oxidation of drimenol 1 with SeO_2. Freshly sublimed SeO_2 (80 mg, 0.72 mmol) was added to a solution of drimenol **1** (100 mg, 0.45 mmol) in 2.5 mL of EtOH and the mixture was refluxed for 5 h. The reaction mixture was poured into water (25 mL) and extracted with ether (3×20 mL). The etheral extract was washed with an aqueous solution of Na_2S (5×5 mL) and water (2×5 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The residue (119 mg) was chromatographed on a column with silica gel L 40/100 (3.6 g). Elution with a hexane—ether mixture (85 : 15) gave 47 mg (44%) of drim-7-ene-9α,11-diol (**10**), m.p. 82—83 °C (from hexane), $[\alpha]_D^{22}$ −100° (*c* 1.0) (*cf.* Ref. 14: m.p. 72—73 °C (from hexane), $[\alpha]_D$ −104°). IR,

ν/cm^{-1}: 875, 1654 (C=CH), 1060, 3440 (br), 3635 (OH). ^{1}H NMR, δ: 0.83 (s, 3 H, C(15)H$_3$); 0.90 (s, 3 H, C(13)H$_3$); 0.93 (s, 3 H, C(14)H$_3$); 1.76 (s, 3 H, C(12)H$_3$); 3.60, 3.77 (both d, 1 H each, AB system, C(11)H$_2$, J = 11.0 Hz); 5.58 (m, 1 H, C(7)H). ^{13}C NMR, δ: 15.14 (C(15)); 18.50 (C(2)); 20.20 (C(12)); 22.20 (C(13)); 23.47 (C(6)); 31.51 (C(1)); 32.96 (C(4)); 33.36 (C(14)); 40.74 (C(10)); 41.64 (C(3)); 42.74 (C(5)); 62.30 (C(11)); 75.45 (C(9)); 127.41 (C(7)); 135.16 (C(8)). The ^{1}H and ^{13}C NMR spectra were identical to those reported previously.[4,14] Found: mol. weight 238.1928 [M]$^+$. $C_{15}H_{26}O_2$. Calculated: mol. weight 238.1933. MS, m/z (I_{rel} (%)): 238 [M]$^+$ (4), 220 [M – H_2O]$^+$ (18), 207 [M – CH_2OH]$^+$ (69), 124 [M – $C_6H_{10}O_2$]$^+$ (26) (retro-Diels—Alder reaction), 123 [M – $C_6H_{11}O_2$]$^+$ (49), 114 [$C_6H_{10}O_2$]$^+$ (100) (retro-Diels—Alder reaction), 109 [M – $C_6H_{10}O_2$ – CH_3]$^+$ (93).

The subsequent elution with a hexane—ether mixture (70 : 30) afforded 10 mg (8%) of 7α-ethoxydrim-8-en-11-ol (**12**), m.p. 138—139 °C (from hexane), $[\alpha]_D^{20}$ +87 (*c* 0.7). IR, ν/cm^{-1}: 1670 (>C=C<), 1080, 3420 (br), 3630 (OH). ^{1}H NMR, δ: 0.86 (s, 3 H, C(15)H$_3$); 0.90 (s, 3 H, C(13)H$_3$); 0.95 (s, 3 H, C(14)H$_3$); 1.23 (m, 3 H, OCH$_2$C<u>H</u>$_3$, J = 7.0 Hz); 1.84 (s, 3 H, C(12)H$_3$); 3.35—3.51, 3.60—3.75 (both m, 1 H each, C(12)H$_2$); 3.52 (br.s, 1 H, C(7)H); 4.10 (q, 2 H, OC<u>H</u>$_2$Me, J = 11.5 Hz). ^{13}C NMR, δ: 15.75 (C(15)); 16.96 (OCH$_2$<u>C</u>H$_3$); 18.79 (C(2)); 18.82 (C(12)); 21.60 (C(13)); 23.49 (C(1)); 32.82 (C(14)); 32.87 (C(4)); 35.97 (C(1)); 38.83 (C(10)); 41.28 (C(3)); 45.84 (C(5)); 58.25 (C(11)); 64.68 (O<u>C</u>H$_2$Me); 77.53 (C(7)); 131.68 (C(8)); 145.43 (C(9)). Found: mol. weight. 226.2248 [M]$^+$. $C_{17}H_{30}O_2$. Calculated: mol. weight. 266.425. MS, m/z (I_{rel} (%)): 266 [M]$^+$ (7), 251 [M – CH_3]$^+$ (15), 236 [M – 2 CH_3]$^+$ (16), 235 [M – CH_2OH]$^+$ (100), 119 [M – CH_3 – CH_3OH]$^+$ (25), 109 [M – $C_9H_{17}O_2$]$^+$ (11).

The subsequent elution with a hexane—ether mixture (55 : 45) gave 37 mg (35%) of drim-7-en-11,12-diol (**11**), m.p. 69.5—70 °C (from hexane), $[\alpha]_D^{20}$ –7.5° (*c* 2.0) (*cf.* Ref. 15: m.p. 69.5—70.5 °C (from hexane), $[\alpha]_D^{22}$ –6.3°). IR, ν/cm^{-1}: 815, 1655, 3045 (C=CH), 1025, 3300 (br, OH). ^{1}H NMR, δ: 0.76 (s, 3 H, C(10)H$_3$); 0.87, 0.88 (both s, 2×3 H, C(4)Me$_2$); 2.95 (s, 2 H, 2 OH); 3.67 (dd, 1 H, C(11)H, J = 8.3 Hz, J = 10.8 Hz); 3.91 (dd, 1 H, C(11)H, J = 1.8 Hz, J = 10.8 Hz); 3.97, 4.35 (both d, 2 H each, AB-system, C(12)H$_2$, J = 12.0 Hz); 5.80 (m, 1 H, C(7)H). ^{13}C NMR, δ: 14.53 (C(15)); 18.79 (C(2)); 21.91 (C(13)); 23.56 (C(6)); 32.97 (C(4)); 33.18 (C(14)); 35.60 (C(10)); 39.32 (C(1)); 42.00 (C(3)); 49.38 (C(5)); 54.44 (C(9)); 61.48 (C(11)); 67.50 (C(12)); 127.49 (C(7)); 136.92 (C(8)). The ^{1}H and ^{13}C NMR spectra are in good agreement with those published previously.[15—17] Found: mol. weight 238.1934 [M]$^+$. $C_{15}H_{26}O_2$. Calculated: mol. weight 238.1933. MS, m/z (I_{rel} (%)): 238 [M]$^+$ (5), 220 [M – H_2O]$^+$ (6), 207 [M – CH_2OH]$^+$ (13), 124 [M – $C_6H_{10}O_2$]$^+$ (29) (retro-Diels—Alder reaction), 109 [M – $C_6H_{10}O_2$ – Me]$^+$ (100).

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