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Tobacco Chemistry. 25. Two New Drimane Sesquiterpene Alcohols from Greek *Nicotiana tabacum* L.

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Two new sesquiterpene alcohols, isolated from Greek tobacco, were shown to be driman-8-ol (*3*) and driman-8,11-diol (*5*) on the basis of spectral data and confirmatory synthesis from drim-7-en-11-ol.**

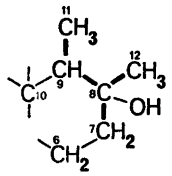
Our continued investigation of the neutral fractions from the volatile extracts of Greek tobacco [1,2] has led to the isolation of two new bicyclic sesquiterpene alcohols.

The first compound, $C_{15}H_{28}O$, was isolated by a combination of liquid and preparative gas chromatography from a fraction of medium polarity (B-5).[2] The presence of a tertiary methyl carbinol group ($>C(OH)CH_3$) followed from IR (3400 cm^{-1}) and NMR data, *i.e.* a methyl singlet at 1.11 ppm and absence of signals downfield of 2.0 ppm. Singlets for three methyl groups at 0.82, 0.82, and 0.88 ppm and a doublet for a methyl group at 0.89 ppm (J 7 Hz) were also observed and with no evidence for unsaturation, these results indicated a bicyclic structure.

On addition of $Eu(dpm)_3$-d_{27}, the three-proton singlet due to the methyl on the hydroxylated carbon suffered the strongest downfield shift. Three one-proton multiplets also moved downfield strongly and must correspond to three protons on the two carbons, vicinal to the hydroxylated carbon. One of these appeared as a distinct quartet (J 7 Hz) and, as shown by spin decoupling, was attached to the same carbon as the methyl group which gave rise to the doublet (7 Hz). The absence of any other measurable couplings to this proton suggested that both carbons adjacent to the carbon carrying it were quaternary. The other two strongly downfield-shifted one-proton multiplets were assigned to the protons of a methylene group. These were mutually coupled (J_{gem} 12 Hz) and since they were both further coupled to two other vicinal protons, there must be an ethylene group linked to the methyl carbinol group. These results furnished the partial structure *1*.

Available evidence, including the fact that the C_5-unit shown in *1* by heavy lines corresponds to a terminal isoprene unit, indicated that this C_{15}-compound was derived from a normal, head-to-tail linked sesquiterpenoid precursor and hence suggested the partial structure *2*. The ring closure between C(9) and C(10) in *2* (numbering as in the final structure *3*) to incorporate the partial structure *1* is directed by

** Nomenclature and stereochemistry as defined in Ref. 3.



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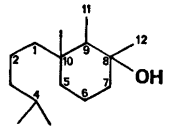

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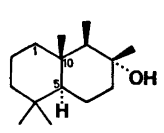

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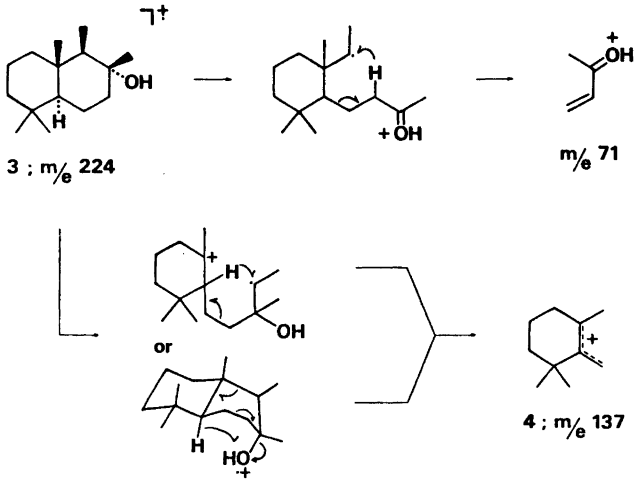
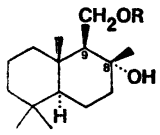
the NMR spectral requirements of (i) a secondary carbon atom at C(9) adjacent to a quaternary carbon atom at C(10), and (ii) that the remaining methyl groups not characterized in the partial structure *1* are at quaternary carbon atoms. The location of the methyl at C(10) is supported by the relative LIS (1.0) observed for a methyl singlet in the NMR spectrum. Cyclisation of *2* at C(4)–C(5) to yield the drimane [3] sesquiterpenoid *3* (no stereochemistry implied) maintains the necessary quaternary centre at C(4) and is preferred to the two remaining alternatives, *i.e.* the bicyclic structures derived by cyclisation of C(4) to C(1) or C(2), because of the mass spectrometric fragmentation pattern. Thus readily explained on the basis of structure *3* are the base peak at *m/e* 71, mainly due to a $C_4H_7O^+$ fragment evidently formed as shown [4] in Scheme 1 through initial α-cleavage of the C(8)–C(9) bond, and the prominent peak at *m/e* 137, characteristic [5] for structurally related labdane diterpenoids (ring A fragment 4). Fragments expected to be prominent on the basis of the alternative structures are insignificant or absent, *e. g.* ions derived by C(1)–C(10) cleavage or formed by reactions initiated by α-cleavage of the C(7)–C(8) bond.

The stereochemical assignments shown in *3* were derived from an analysis of the NMR spectrum after the addition of $Eu(dpm)_3$-d_{27}. C(9)H is coupled only to $C(11)H_3$ and the absence of any long-range W-coupling [6] to the equatorial proton at C(7) indicates that C(9)H is axial. The observed LIS for the methyl groups at C(8), C(9), and C(10) are in the order 2.6:1.8:1.0 and this can be rationalized only by co-ordination of the lanthanide complex to an equatorial C(8)OH group. The relatively weak LIS observed for the methyl groups at C(4) (0.4 axial; 0.2 equatorial) relative to the LIS (1.0) measured for the $C(10)CH_3$ support a *trans*-fused geometry of the rings. The synthesis of *3* (*vide infra*) from drim-7-en-11-ol (*9*) confirms the structure *3*, with stereochemistry as shown, for this tobacco compound.

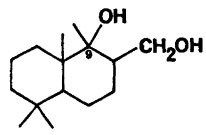
The second compound was isolated by liquid chromatography from a less volatile, neutral fraction of the Greek tobacco extract and purified as the acetate. The latter was the monoacetate of a diol, $C_{15}H_{28}O_2$, as shown by IR absorption at 3470, 1740, and 1243 cm^{-1} and NMR signals at 2.04 ppm (3 H, s) and 5.4 ppm (1 H, broad s, removed by D_2O). Resonances at 4.26 ppm (1 H, dd, *J* 5.5 and 12 Hz) and 4.36 ppm (1 H, dd, *J* 4.5 and 12 Hz), shifted upfield to 3.90 ppm (2 H, m) in the diol, showed the presence of a primary acetate [7] attached to a secondary carbon ($>CH\text{-}CH_2OCOCH_3$). The NMR spectrum of the diol also exhibited singlets for three methyl groups at 0.81, 0.81, and 0.88 ppm and a downfield singlet at 1.33 ppm for a methyl attached to a tertiary carbinol group. With no evidence of unsaturation, these data implied a C_{15} compound having five C_1-substituents on a bicyclic C_{10}-nucleus and hence a drimane skeleton, which made only two alter-



Scheme 1.



5 R = H
6 R = $COCH_3$



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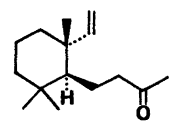

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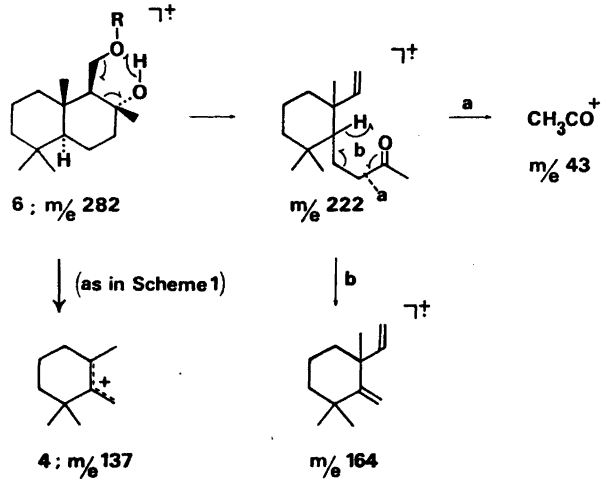
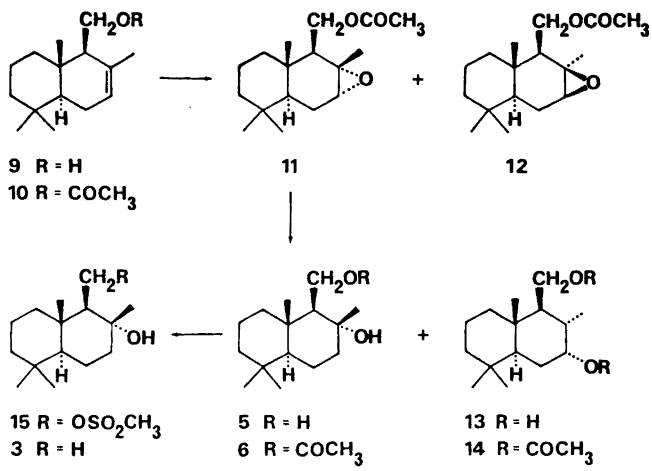
native structures, neglecting stereochemistry, worthy of consideration, namely driman-8,11-diol (*5*) and driman-9,12-diol (*7*). The mass spectra of the diol and the acetate – both displaying the expected *m/e* 137 ion ($C_{10}H_{17}$) corresponding to the drimane ring A fragment 4 – allowed these to be distinguished. Thus the *m/e* 222 ion, due to a $C_{15}H_{26}O$ fragment formed by loss of CH_3COOH from the acetate and water from the diol, underwent loss of acetone to give a *m/e* 164 ion ($C_{12}H_{20}$, m*), a reaction only readily explained in terms of structure *5* (Scheme 2). Moreover, the structures given for the *m/e* 222 and 164 species in Scheme 2 are supported by the fact that the spectra of the diol and the acetate below *m/e* 222 are very similar, except for the *m/e* 137 peak, to that of the ketone *8*. The structure 5, with stereochemistry as shown, was established by synthesis.

It was envisaged that a successful synthesis of the diol *5* would in turn permit the convenient preparation of the alcohol *3* and the synthetic routes to these compounds from drim-7-en-11-ol (9) are outlined in Scheme 3. 11-Acetoxydrim-7-ene (*10*) was treated with *m*-chloroperbenzoic acid in methylene chloride at $-30°$ for three days to give an excellent yield of the desired α-epoxide *11*, formed by preferential attack from the sterically less hindered α-side, and minor amounts of the less polar, and chromatographically readily removed, β-epoxide *12*. Reductive opening of the α-epoxide *11* with excess $LiAlH_4$ in refluxing ether (36 h) gave the diol *5*, identical in all respects with the natural product. However, the yield of the diol *5* was low and the major product was the previously prepared [3] diol *13*, the result of preferred *trans*-diaxial opening of the oxirane ring. Since Ohloff *et al.*[11] have recently shown that in the corresponding 11-nor compound steric hindrance by the $C(10)CH_3$ leads preferentially to abnormal ring opening (nucleophilic attack at C(7) giving the equatorial 8 α-alcohol), it seems that in the acetoxyepoxide



Scheme 2.



Scheme 3.

11 this steric effect is outweighed by a directing influence of the primary oxygen function on the nucleophile. An anchimeric assistance by the hydroxyl group in the ring cleavage reaction such as recently observed by Barton *et al.*[12] for 4α,5α-epoxy-7α-hydroxy steroids, which would also favour the abnormal opening, is unlikely to be of importance in the present case.

Overnight reaction of the diol *5* with excess methanesulphonyl chloride in pyridine at 0° gave a quantitative yield of the monomesylate *15*. Subsequent reduction with $LiAlH_4$ furnished in good yield the alcohol *3*, identical in all respects with the corresponding natural product.

We have previously isolated from Greek tobacco a number of compounds which may be degradation and/or rearrangement products of terpenoid precursors.[8,9,13] The two new compounds (*3* and *5*) are of interest in this context as they both represent potential precursors of the vinylketone *8*, previously also obtained by us from Greek tobacco;[8] *i.e.* from driman-8,11-diol (*5*) by 1,3-diol-rearrangement, and/or from driman-8-ol (*3*) by oxidative fragmentation. Attempts to prepare the vinylketone *8* by oxidation of driman-8-ol (*3*) in refluxing cyclohexane in the presence of calcium carbonate gave, however, only a small quantity of *8*, as detected by GC-MS and TLC.

EXPERIMENTAL

NMR, IR, and mass spectra were recorded on Varian HA100D and XL-100, Digilab FTS-14 and Perkin-Elmer 257, and LKB 9000 (70 eV) instruments, respectively. Rotations were measured on a Perkin-Elmer 141 instrument and accurate mass determinations were carried out at the Laboratory for Mass Spectrometry, Karolinska Institutet, Stockholm.

Isolations. Driman-8-ol (*3*) (12 mg) was isolated by column chromatography on silica and silica impregnated with 20 % $AgNO_3$ followed by preparative gas chromatography (3 m × 3.2 mm glass column packed with 5 % Carbowax 20 M on Chromosorb G) from the volatile neutral fraction B-5 of an extract of the leaves of sun-cured Greek *Nicotiana tabacum* L.[1] Driman-8,11-diol (*5*) was isolated as the acetate derivative (*6*) (11 mg) (after acetylation of a complex sub-fraction with excess acetic anhydride in pyridine for 24 h at room temperature) by liquid chromatography on silica from a medium-volatile neutral fraction of the leaves of sun-cured Greek *N. tabacum L.* The fractionation of this medium-volatile material will be described later.[2]

Driman-8-ol (*3*). Colourless needles m.p.73–75° (early softening). MS: 224 (M^+, 8 %), 71 (100), 69 (70), 83 (70), 97 (66), 43 (63), 109 (62), 55 (61), 41 (60), 95 (56); accurate mass measurement: $C_{15}H_{28}O$, found 224.2140, calc. 224.2140; $C_{10}H_{17}$, found 137.1320, calc. 137.1330; C_4H_7O, found 71.0499, calc. 71.0497; C_5H_{11}, found 71.0863, calc. 71.0861, *m/e* 71.0499 and 71.0863 peaks are of approximately equal intensities; $\delta(CDCl_3)$ 0.82 (6 H, s, C(4β)CH_3 and C(10β)CH_3), 0.88 [3 H, s, C(4α)CH_3], 0.89 [3 H, d, J ~7 Hz, C(9β)CH_3], 1.11 [3 H, s, C(8β)CH_3]; on addition of Eu(dpm)$_3$-d_{27}, r (relative induced shift ra-

tio) = 0.2 [3 H, s, C(4α)CH_3], 0.4 (3 H, s, C(4β)CH_3), 1.0 [3 H, s, C(10β)CH_3], 1.8 (3 H, d, J 7 Hz, C(9β)CH_3), 2.6 (3 H, s, C(8β)CH_3, 3.6 (1 H, q, J 7 Hz, C(9α)H), 3.4 (1 H, d of t, J ~3, 12 Hz, C(7β)H), ~4.0 (1 H, broad t of d, J ~4, 12 Hz, C(7α)H); ν_{max}(KBr) 3400 (broad), 1078 (m), 1058 (w), 940 (w) cm^{-1}; $[\alpha]_D^{20}$ −18.2° (c 0.56, $CHCl_3$).

11-Acetoxydriman-8-ol (*6*). M.p. 77 – 79° (early softening): MS: 282 (M^+, 3 %), 43 (100), 41 (30), 95 (28), 109 (28), 69 (26), 55 (24), 82 (23), 81 (22), 123 (18); accurate mass measurement: $C_{17}H_{30}O_3$, found 282.2202, calc. 282.2195; $C_{15}H_{26}O$, found 222.1986, calc. 222.1984; $C_{12}H_{20}$, found 164.1568, calc. 164.1565; C_5H_6O, found 82.0415, calc. 82.0419; C_6H_{10}, found 82.0785, calc. 82.0782; δ ($CDCl_3$) 0.82 (3, H, s), 0.87 (3 H, s), 0.89 (3 H, s), 1.18 (3 H, s), 2.04 (3 H, s), 4.26 (1 H, dd, J 5.5, 12 Hz), 4.36 (1 H, dd, J 4.5, 12 Hz), 5.4 (1 H, broad); ν_{max}(film) 3470 (broad), 1740 (s), 1243 (s), 1030 (w) cm^{-1}; $[\alpha]_D^{20}$ −9° (c 0.53, $CHCl_3$).

Driman-8,11-diol (*5*). Colourless crystals m.p. 119 – 120°. MS: 240 (M^+, 0.5 %), 43 (100), 95 (84), 109 (79), 69 (72), 82 (72), 123 (60), 164 (60), 41 (58), 81 (56), 55 (54); δ($CDCl_3$) 0.81 (6 H, s), 0.88 (3 H, s), 1.33 (3 H, s), 3.9 (2 H, m); ν_{max} (KBr) 3360 (broad), 1076 (w), 1053 (w), 1023 (m), 1015 (w), 994 (w), 940 (w), 913 (w) cm^{-1}; $[\alpha]_D^{20}$ 1.6° (c 0.63, $CHCl_3$).

7α,8-Epoxy-11-acetoxydrimane (*11*). 11-Acetoxydrim-7-ene (*10*) was prepared by overnight reaction of drim-7-en-11-ol (*9*) (1.1 g) with excess acetic anhydride (2.4 g) in pyridine solution (7 ml) at room temperature. TLC showed the crude acetylated product *10* (1.27 g) to be essentially pure and it was used in the next step without further purification. A solution of *m*-chloroperbenzoic acid (1.1 g) in methylene chloride (20 ml) was added dropwise over 2 h to a cold (−30°) stirred solution of *10* (1.27 g) in methylene chloride (50 ml). After 3 days at −30° TLC showed the reaction mixture contained no unreacted *10* and the reaction mixture was diluted with ether, washed with saturated $NaHCO_3$ solution, water and dried (Na_2SO_4). Evaporation of the solvent gave a colourless oil (1.36 g) which crystallized slowly on standing and TLC (SiO_2; 40 % ether/hexane) revealed a mixture of two products (R_F 0.33 and 0.36) in the ratio 9:1. The more polar major product, the α-epoxide *11*, was purified by chromatography on silica: m.p. 55 – 57°; MS: 280 (M^+, 5 %), 99 (100), 43 (91), 123 (42), 69 (42), 41 (41), 85 (38), 124 (38), 71 (36), 55 (32), 73 (28); δ($CDCl_3$) 0.83 (3 H, s), 0.87 (3 H, s), 0.89 (3 H, s), 1.36 (3 H, s), 2.07 (3 H, s), 3.00 (1 H, m, $w_{1/2}$ 4 Hz), 4.0 (1 H, dd, J 9.5, 12 Hz), 4.4 (1 H, dd, J 3, 12 Hz); ν_{max} (KBr) 1740 (s), 1240 (s), 1045 (m), 1036 (m) cm^{-1}; $[\alpha]_D^{20}$ 29.3° (c 0.41, $CHCl_3$).

11-Acetoxydriman-8-ol (*6*) and *7α,11-diacetoxy-8α-drimane* (*14*). Excess $LiAlH_4$ (0.6 g) was added to a solution of the α-epoxide *11* (1.3 g) in dry ether (100 ml) and the mixture was heated under reflux for 30 h. The cooled reaction mixture was treated with ethyl acetate to decompose unreacted $LiAlH_4$, diluted with ether and washed with 1 M HCl, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). Evaporation of the solvent gave a crystalline residue (1.1 g) which was treated overnight at room temperature with acetic anhydride (3 g) in pyridine solution (6 ml). Methanol (0.5 ml) was added (at 0°) to decompose excess acetic anhydride (15 min) and the reaction mixture was diluted with ether and washed with 1 M HCl, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). Evaporation of the ether gave a colourless oil (1.3 g) which TLC (SiO_2; 60 % ether/hexane) indicated contained some unreacted starting material (*11*) and two products R_F 0.59 and 0.35). Column chromatography on silica (110 g) recovered unreacted *11* (190 mg) and separated the reaction products. The less polar major product (800 mg) was the diacetate *14* isolated as a low-melting crystalline solid. MS: M^+ not visible, 43 (100 %), 204 (84), 189 (61), 119 (38), 69 (34), 121 (30), 55 (28), 41 (26), 81 (26), 109 (16); δ($CDCl_3$) 0.80 (3 H, s), 0.82 (3 H, s), 0.89 (3 H, d, J 6.5 Hz), 0.90 (3 H, s), 2.02 (3 H, s), 2.06 (3 H, s), 4.06 (1 H, dd, J 3, 12 Hz), 4.18 (1 H, dd, J 3, 12 Hz), 5.04 (1 H, m, $w_{1/2}$ 6 Hz); ν_{max} (KBr) 1740 (s), 1240 (s), 1025 (m) cm^{-1}; $[\alpha]_D^{20}$ −37.6° (c 0.51, $CHCl_3$).

The more polar product (97 mg) was the acetate *6*, isolated as a colourless oil that crystallised on standing and identical in all respects to the acetate *6* of the tobacco compound *5*.

Driman-8,11-diol (*5*). Hydrolysis of the synthetic acetate *6* in 10 % methanolic KOH (10 min) and work-up as described above gave synthetic *5* indistinguishable from the diol *5* isolated from the tobacco.

Driman-8-ol-11-yl methane sulphonate (*15*). A cold (0°) solution of the diol *5* (18 mg) in dry pyridine (1 ml) was treated with methanesulphonyl chloride (25 mg) and after 18 h at 0 – 5° excess methanesulphonyl chloride was decomposed with a few drops of water, the reaction mixture was diluted with ether and washed with 1 M HCl, saturated $NaHCO_3$ solution, brine, dried (Na_2SO_4) and the solvent evaporated to leave a pale yellow oil (24 mg). This product showed a single spot on TLC (SiO_2; 80 % ether/hexane) and was used in the next step without further purification. δ($CDCl_3$) 0.82 (3 H, s), 0.90 (6 H, s), 1.15 (3 H, s), 2.1 (1 H, broad s), 3.02 (3 H, s), 4.32 (2 H, dd, J 6, 11 Hz), 4.55 (2 H, dd, J 3, 11 Hz); ν_{max} (film) 3500 (broad), 1355 (s), 1175 (s), 945 (s) cm^{-1}.

Driman-8-ol (*3*). The crude mesylate *15* (24 mg) in dry ether solution (5 ml) was treated with $LiAlH_4$ (40 mg) and the mixture refluxed for 18 h. Ethyl acetate was added to the cooled reaction mixture to decompose excess $LiAlH_4$ and the mixture was diluted with ether and washed with 1 M HCl, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). The solvent was evaporated to leave a crystalline residue (18 mg) which was chromatographed on silica to recover

diol *5* (7 mg), and isolate synthetic *3* (11 mg) which was identical in all respects to the tobacco compound *3*.

Oxidation of driman-8-ol (3). Driman-8-ol (4 mg) was added to a mixture of $CaCO_3$ (5 mg) and $Pb(OAc)_4$ (20 mg) in cyclohexane (2 ml) and the mixture heated under reflux for 24 h. Direct analysis of the reaction mixture by GLC-MS revealed about 70 % unreacted *3* and a minor component (~5 %) with a mass spectrum and retention time (50 m × 0.3 mm glass column coated with HB 5000) identical to that of authentic vinylketone *8*.

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