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ELIMINATION OF C-8-FUNCTIONAL GROUPS FROM DRIMAN-8α,11-DIOL-11-MONOACETATE AND -DIACETATE

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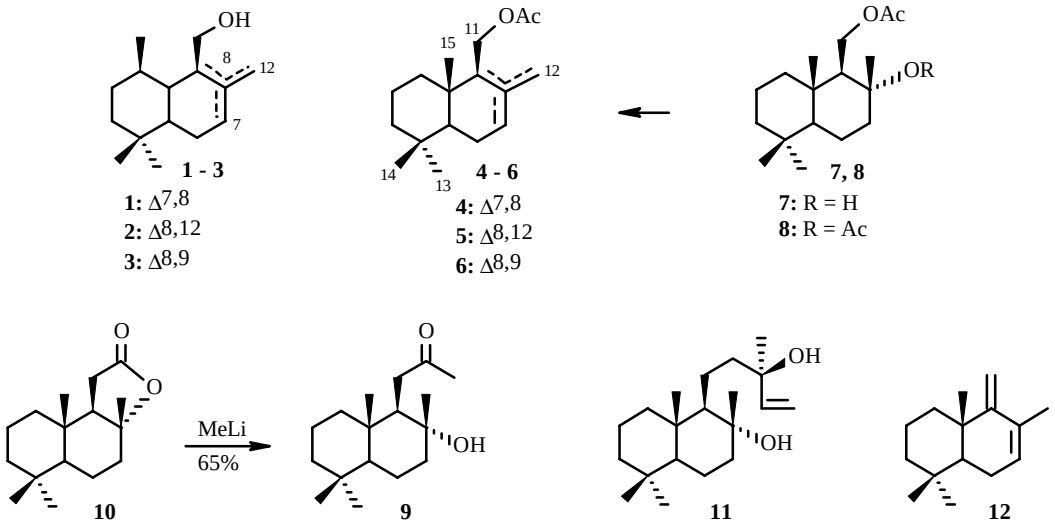
The dehydration products of driman-8α,11-diol-11-monoacetate that are formed upon reaction with several dehydrating agents and the products from elimination of the C-8 acetoxy group in driman-8α,11-diol diacetate were investigated in detail. A new effective synthesis of drimenylacetate from driman-8α,11-diol-11-monoacetate by its regioselective dehydration using methanesulfonic acid trimethylsilyl ether was developed.

Key words: drimanes, driman-8α,11-diol-11-monoacetate, driman-8α,11-diol diacetate, dehydration, cleavage, drimenylacetate, albicanylacetate, isodrimenylacetate.

The drimane sesquiterpene alcohols drimenol (**1**), albicanol (**2**), and isodrimenol (**3**) and their acetates **4-6** are important starting compounds for synthesizing various biologically active natural compounds [1-5] whereas drimenol (**1**) and albicanylacetate (**5**) themselves are biologically active [1, 6]. Therefore, the development of synthetic methods for these compounds is of definite scientific interest.



One of the important and attractive synthetic pathways to **4-6** is the elimination of a C_8-functional group from the 11-monoacetate (**7**) or the diacetate of driman-8α,11-diol (**8**). Driman-8α,11-diol-11-monoacetate (**7**) is readily available. We synthesized it previously in quantitative yield via peracid oxidation of 11-bishomodriman-8α-ol-12-one (**9**) [7], which was prepared from norambreinolide (**10**), the cleavage product of many labdane diterpenoids [8], or via ozonolytic cleavage of sclareol (**11**) [9]. Driman-8α,11-diol diacetate (**8**), in turn, can be prepared in greater than 90% yield via the literature method [6].

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TABLE 1. Products and Conditions of the Dehydration Reaction

Starting material	Reagent and reaction conditions (method)	Total yield of acetates (**4**-**6**), %	Ratio of acetates (**4**-**6**), %	Yield of hydrocarbon (**12**), %
Driman-8α,11-diol-11-monoacetate (**7**)	(a) $Sc(OTf)_3$ (10 mol%), AcOH, 18-20°C	65	59:13:28	8
7	(b) $Sc(OTf)_3$ (1 eq.), CH_3CN, 18-20°C	61	75.5:15.5:9	15
7	(c) $CF_3SO_3SiMe_3$ (1 eq.), CH_3CN, 18-20°C	66	90:9:1	16
7	(d) PCl_5 (2 eq.), Et_2O, 0°C	74	28:20:52	3
7	(e) PCl_5 (5 eq.), Py, 0°C	76	28:49:23	2
7	(f) Amberlyst-15, (1:1), CH_2Cl_2, 18-20°C	72	63:21:16	14
Driman-8α,11-diol diacetate (**8**)	(a) SiO_2 Merck (1:10), hexane, Δ	75	56:39:5	19
8	(b) DMSO, $NaHCO_3$, 140-160°C	77	25:53:22	4

Obviously it would be interesting to perform regioselective elimination of a C_8-functional group of **7** or **8** to form only one of the possible acetates (**4**-**6**). The use of several reagents to achieve this goal has been reported. Thus, hydroxyacetate **7** was dehydrated with $POCl_3$ in pyridine. The composition of the reaction products was not studied in detail. TLC gave two spots. The products of its alkaline saponification were separated by preparative TLC, which isolated drimenol (**1**) in 40% yield.

Poigny et al. [11] dehydrated **7** with an excess of $SOCl_2$ in pyridine in the presence of 4-dimethylaminopyridine (DMAP) and produced a mixture of acetates (**4**-**6**) in which albicanylacetate (**5**) predominated. Oxidation of this mixture by *m*-chloroperbenzoic acid gave the epoxides of **4** and **6** whereas albicanylacetate (**5**) was unchanged and isolated chromatographically in 61% yield.

Barrero et al. [6] produced equimolar mixtures of **4**-**6** via dehydration of **7** by $POCl_3$ in pyridine or by mesylchloride in Et_3N in the presence of DMAP. Dehydration of **7** by $SnCl_4$ (CH_2Cl_2, -19°C) proceeded regioselectively to form drimenylacetate (**4**) in low yield (25%).

Heating **8** in collidin [6] produced in quantitative yield an equimolar mixture of albicanyl- and isodrimenylacetates (**5**) and (**6**).

We previously synthesized drimenol (**1**) from the monoacetate **7** in one step in greater than 50% yield via treatment with ethanolic H_2SO_4 [12]. We also dehydrated **7** with $POCl_3$ in pyridine to produce a mixture of acetates **4**-**6** in a 46:40:14 ratio [12]. In continuation of this work, we studied in detail the composition of products from reaction of **7** with trimethylsilylmethanesulfonate $MeSO_3SiMe_3$, trimethylsilyltrifluoromethanesulfonate $CF_3SO_3SiMe_3$, scandium trifluoromethanesulfonate $Sc(CF_3SO_3)$, PCl_5, and ion-exchange resin Amberlist-15 and also the products formed from **8** on heating in DMSO in the presence of $NaHCO_3$ and on boiling in hexane with Merck silica gel.

The reaction of **7** with $MeSO_3SiMe_3$ in CH_3CN gave a single product from elimination of the C_8-hydroxyl, drimenylacetate (**4**, 65-70% yield), regardless of the mass ratio of **7** and the reagent (1.5 eq. or 5 eq.). The reagent:substrate ratio affected only the reaction rate (2 h or 10 min, respectively). Besides **4**, a diene hydrocarbon (**12**) was also formed (14-17% yield).

Reaction of **7** with the remaining reagents mentioned above and pyrolysis of **8** produced mixtures of unsaturated acetates (**4**-**6**) and the hydrocarbon (**12**). Table 1 gives the ratios of acetates (**4**-**6**) determined using PMR spectra, their total yield, the yield of **12**, the reagents, and the optimal conditions.

Reaction of **7** with an excess of $CF_3SO_3SiMe_3$ (3.9 eq.) in CH_3CN at 18-20°C was completed very quickly (10 min) and formed **12** as the single product. However, a mixture of acetates (**4**-**6**) with **4** dominating substantially [Table 1, method (c)] was produced by the optimal version using 1 eq. of reagent and carrying out the reaction first on an ice bath and then at 18-20°C. The amount of reagent (10 mol% or 1 eq.) and the solvent had a significant effect on the reaction rate and the ratio of produced acetates (**4**-**6**) for reaction of **7** with $Sc(OTf)_3$. Thus, the reaction occurred at 18-20°C after 22 h in AcOH with 10 mol% $Sc(OTf)_3$ whereas 50% of the starting material remained unchanged in CH_3CN after 48 h. However, if the reaction was carried out in CH_3CN with 1 eq. of $Sc(OTf)_3$, then it was finished in 2 h. The ratio of isomers (**4**-**6**) also varied considerably [Table 1, methods (a) and (b)].

The solvent also played an integral role in the reaction of **7** with PCl_5. Thus, the reaction was quicker in ether (3 h) than in pyridine (6 h) with cooling in an ice bath and use of the same amount (2 eq.) of PCl_5. The yields of acetates **4**-**6** were practically the same although their ratios were different. Isodrimenylacetate (**6**) dominated the mixture of acetates **4**-**6** for the reaction in ether [Table 1, method (d)] whereas use of 5 eq. of PCl_5 in pyridine changed the ratio in favor of albicanylacetate (**5**) [Table 1, method (e)].

As expected, the mass ratio of **7** and Amberlist-15 had a distinct effect on the reaction rate. Thus, the reaction was complete after 24 h for a 10:1 ratio; 17 h, for 5:1; and 1 h 45 min, for 1:1. In all instances a mixture of acetates **4**-**6** was formed [Table 1, method (f)]. However, the reaction was complete after 1.5 h for a 1:10 substrate:Amberlist-15 ratio although the only product was **12**.

A study of the reaction of **8** with Merck silica gel found that the reaction practically did not occur at 18-20°C. A mass ratio of 1:10 was optimal on boiling in hexane. The reaction was complete after 3 h whereas with a 1:5 ratio more than 7 h was required. In this instance drimenylacetate (**4**) dominated the mixture of acetates **4**-**6**.

Thus, cleavage of the C_8-functional group in **7** and **8** formed in most instances in good yields mixtures of acetates **4**-**6** (Table 1) with drimenylacetate (**4**) being the main product in most methods. Drimenylacetate (**4**) was the only product of dehydration of **7** by $MeSO_3SiMe_3$ (65-70% yield). Albicanylacetate (**5**) dominated (49%) the mixture of acetates **4**-**6** produced by reaction of **7** with PCl_5 in pyridine and by heating **8** in DMSO (53%). Isodrimenylacetate (**6**) dominated for reaction of **7** and PCl_5 in ether (52%).

EXPERIMENTAL

Melting points were determined on a heated Boetius stage. IR spectra of films were recorded on a Specord 74 spectrophotometer. PMR spectra in $CDCl_3$ were recorded on a Bruker AC-E 80 spectrometer. Chemical shifts are given in ppm relative to the resonance of $CHCl_3$ as an internal standard (7.24 ppm). The course of reactions was monitored by TLC on Silufol plates with development by I_2 vapor. Column chromatography used silica gel grade L 100/400 at a 1:20 mass ratio. Ether extracts were dried over anhydrous $MgSO_4$. Reagent-grade $MeSO_3SiMe_3$, Me_3SiOTf, and $Sc(OTf)_3$ were purchased (Aldrich).

Preparation of Drimenylacetate (4) from Drimandiol-11-monoacetate (7). A solution of **7** (100 mg, 0.354 mmol) in CH_3CN (1 mL) was treated with $MeSO_3SiMe_3$ (0.28 mL, 305 mg, 1.81 mmol), stirred for 10 min at 18°C, and treated with water (5 mL) and ether (15 mL). The mixture was transferred to a separatory funnel. The aqueous layer was separated. The ether layer was washed with $NaHCO_3$ solution (3 × 2 mL) and water (3 × 2 mL) and dried. Ether was distilled off in vacuo to produce a liquid product (85 mg) that was chromatographed over a silica-gel column (1.7 g) with elution by hexane to give **12** (12 mg, 17%) and by hexane:ether (49:1) to give **4** (66 mg, 70.5%), the IR and PMR spectra of which agreed fully with those reported [6].

Monoacetate **7** (1 g) produced analogously **12** (100 mg, 14%) and **4** (610 mg, 65%).

Preparation of Drimenol (1) from Drimenylacetate (4). Drimenylacetate (**4**, 590 mg, 2.23 mmol) was treated with KOH in CH_3OH (6 mL, 10%), stirred at 18°C for 1 h, diluted with water (60 mL), and extracted with ether (3 × 40 mL). The extract was washed with water (3 × 10 mL) and dried. The ether was distilled off. The crystalline solid was recrystallized from hexane to afford a product (426 mg, 86%) with mp 93-94°C. The melting point and spectral properties agreed with those for drimenol [12].

Preparation of a Mixture of Acetates (Drimenylacetate, 4; Albicanylacetate, 5; Isodrimenylacetate, 6) from Drimandiol-11-monoacetate (7). Method (a). A solution of **7** (100 mg, 0.354 mmol) in AcOH (0.7 mL) was treated with $Sc(OTf)_3$ (18 mg, 0.037 mmol, 10 mol%), stirred at 18-20°C for 22 h, treated with water (3 mL), neutralized with dry $NaHCO_3$, and extracted with ether (4 × 5 mL). The extract was washed with water (3 × 1 mL) and dried. The ether was distilled off to afford the mixture of products (82 mg) that was chromatographed over a silica-gel column (1.6 g) with elution by hexane to give **12** (6 mg, 8.5%), the PMR spectrum of which agreed with that in the literature [13], and by hexane:ether (49:1) to give a mixture of **4**-**6** (61 mg, 65%) in a 59:13:28 ratio {PMR data, characteristic resonances, δ, ppm, J/Hz: 2.00 (s, 3H, OAc), 3.95-4.37 [m, 2H, $C(11)H_2$], 4.51 and 4.85 (both d, $C=CH_2$, J = 1.41), 5.47-5.51 (m, C=CH)}. The contents of **4** and **6** and their sum were determined by integration; the content of the isomer with the tetrasubstituted double bond (**5**), by difference. IR spectrum, film, cm^{-1}: 830 (>C=CH), 880, 1640, 3100 ($C=CH_2$), 1230, 1735 (OAc).

Method (b). A solution of **7** (100 mg, 0.354 mmol) in CH_3CN (1 mL) was treated with $Sc(OTf)_3$ (180 mg, 0.366 mmol), stirred at 18-20°C for 2 h, diluted with ether (10 mL), washed with water (5 × 1 mL), and dried. Solvent was distilled off in vacuo to give a product (88 mg) that was chromatographed over a silica-gel column (1.8 g) as described in Method (a) to give **12** (11 mg, 15%) and the mixture of acetates (**4**-**6**, 57 mg, 61%) in a 75.5:15.5:9 ratio.

Method (c). A solution of **7** (100 mg, 0.354 mmol) in CH_3CN (1 mL) was cooled in an ice bath, stirred, treated with $CF_3SO_3SiMe_3$ (0.07 mL, 86 mg, 0.387 mmol), stirred another 15 min at 0°C and 20 min at 18-20°C, and treated with water (5 mL) and ether (15 mL). The ether layer was separated, washed with $NaHCO_3$ solution (3 × 2 mL) and water (3 × 2 mL), and dried. Solvent was distilled off in vacuo to afford a product (86 mg) that was chromatographed over a silica-gel column (1.8 g) as described for Method (a) to give **12** (12 mg, 16%) and the mixture of acetates (**4**-**6**, 62 mg, 66%) in a 90:9:1 ratio.

Method (d). A solution of PCl_5 (140 mg, 0.672 mmol) in absolute ether (3 mL) was stirred, cooled in an ice bath, treated with **7** (99 mg, 0.350 mmol) in absolute ether (2 mL), stirred for 3 h, treated dropwise with water (5 mL), diluted with ether (10 mL), and transferred to a separatory funnel. The aqueous layer was separated. The ether layer was washed with $NaHCO_3$ solution (3 × 3 mL) and water (3 × 3 mL) and dried. The ether was distilled off in vacuo. Chromatography of the resulting product (94 mg) over silica gel (1.88 g) as described for Method (a) produced **12** (2 mg, 3%) and the mixture of acetates (**4**-**6**, 69 mg, 74%) in a 28:20:52 ratio.

Method (e). A solution of PCl_5 (375 mg, 1.8 mmol) in dry pyridine (2.5 mL) was stirred, cooled in an ice bath, treated with **7** (100 mg, 0.354 mmol) in pyridine (2.5 mL), stirred another 6 h, treated dropwise with cooling and stirring with H_2SO_4 (10%, 15 mL), and extracted with ether (3 × 10 mL). The extract was washed with H_2SO_4 (10%, 3 mL), water (3 mL), $NaHCO_3$ solution (3 × 5 mL), and water (3 × 5 mL) and dried. Solvent was distilled in vacuo to afford a product (83 mg) that was chromatographed over a silica-gel column (1.68 g) as described for Method (a) to isolate **12** (2 mg, 2%) and the mixture of acetates (**4**-**6**, 71 mg, 76%) in a 28:49:23 ratio.

Method (f). A solution of **7** (108 mg, 0.382 mmol) in CH_2Cl_2 (5 mL) was treated with Amberlist-15 (111 mg), stirred at 18-20°C for 1 h 45 min, filtered, and washed with CH_2Cl_2 (5 mL). The filtrate was evaporated to afford a product (98 mg) that was chromatographed over a silica-gel column (2 g) as described for Method (a) to afford **12** (11 mg, 14%) and the mixture of acetates (**4**-**6**, 73 mg, 72%) in a 63:21:16 ratio.

Preparation of a Mixture of Acetates (Drimenol, 4; Albicanol, 5; Isodrimenol, 6) from Drimandiol Diacetate (8). Method (a). A solution of **8** (100 mg, 0.308 mmol) in hexane (5 mL) was treated with Merck silica gel (1 g) and boiled with stirring for 3 h. The silica gel was filtered off and washed with hexane (5 mL) and separately with ether (10 mL). The hexane filtrate was evaporated to afford **12** (10 mg). The ether filtrate was also evaporated. The resulting residue (65 mg) was chromatographed over a silica-gel column (1.3 g) with elution by hexane to give an additional portion of **12** (2 mg). Total yield 12 mg (19%). Hexane:ether (49:1) eluted the mixture of acetates (**4**-**6**, 61 mg, 75%) in a 56:39:5 ratio.

Method (b). A solution of **8** (100 mg, 0.308 mmol) in DMSO (5 mL) was treated with $NaHCO_3$ (36 mg, 4.28 mmol), heated with stirring at 140-160°C for 10 h, cooled, diluted with water (50 mL), and extracted with ether (3 × 20 mL). The ether extract was washed with water (2 × 10 mL) and dried. The ether was distilled off. The residue (73 mg) was chromatographed over a silica-gel column (1.5 g) as described for Method (a) to afford **12** (3 mg, 4%) and the mixture of acetates (**4**-**6**, 63 mg, 77%) in a 25:53:22 ratio.

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