

SYNTHESIS OF DRIM-9(11)-EN-8 α - AND -8 β -OLS FROM DRIMENOL

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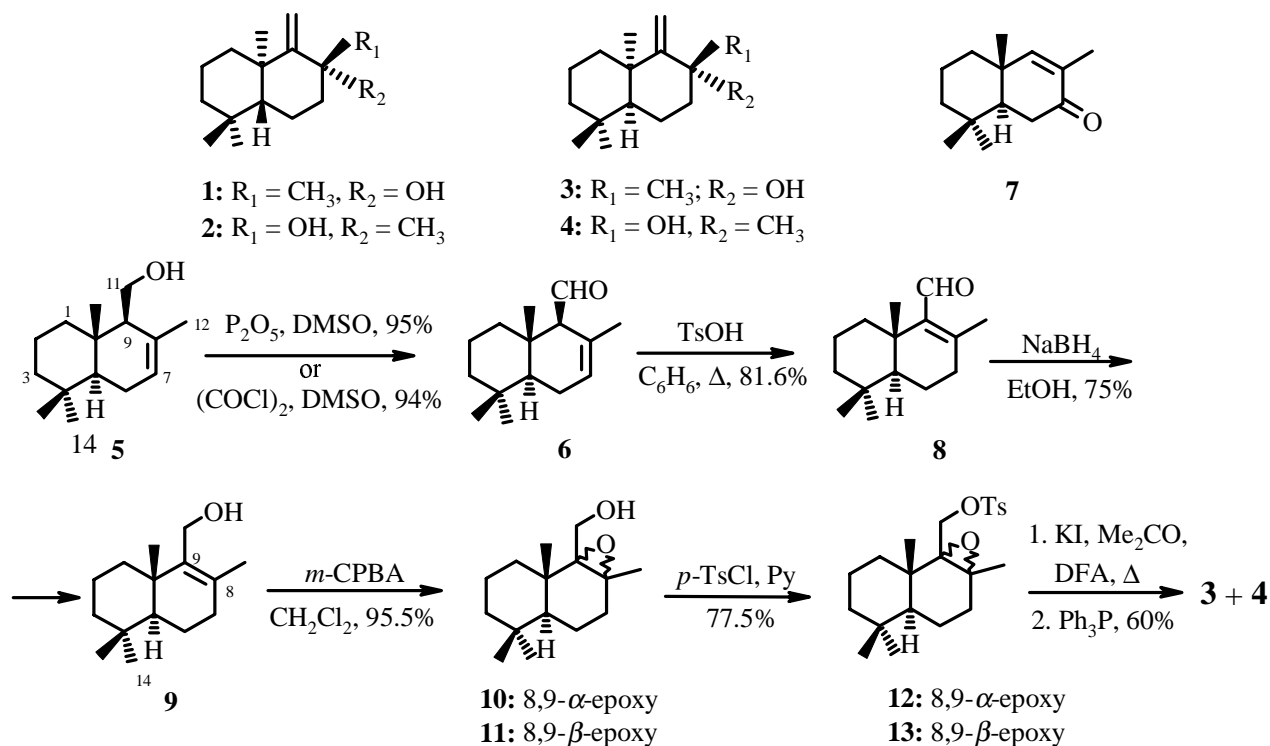
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*Drim-9(11)-en-8 α -ol and drim-9(11)-en-8 β -ol were synthesized in six steps from drimenol. Drimenol was oxidized by P_2O_5 and DMSO to drimenal, which isomerized with *p*-TsOH into isodrimenal. Isodrimenal was reduced by $NaBH_4$ into isodrimenol, epoxidation of which by *m*-CPBA gave a mixture (3.4:1) of α - and β -epoxyisodrimenols. These reacted with tosyl chloride in Py to give a mixture of α - and β -epoxyisodrimenol tosylates. Treatment of the tosylate mixture with KI and then Ph_3P produced a mixture of drim-9(11)-en-8 α - and -8 β -ols that was separated chromatographically. The overall yield was ~26%.*

Key words: synthesis, drim-9(11)-en-8 α -ol, drim-9(11)-en-8 β -ol, drimenol, drimenal, isodrimenal, isodrimenol.

The bicyclic sesquiterpenoids *ent*-drim-9(11)-en-8 α -ol (**1**) and *ent*-drim-9(11)-en-8 β -ol (**2**) occur in certain food products [1]. Several syntheses of the enantiomer of **2**, drim-9(11)-en-8 α -ol (**3**) [2-5] and drim-9(11)-en-8 β -ol (**4**) [6, 7], and the natural compound **1** [6] have been developed from available labdane and *ent*-labdane bicyclic diterpenoids.

Herein we report the synthesis of **3** and **4** from the available drimane sesquiterpenoid drimenol (**5**) according to Scheme 1.



Scheme 1

Oxidation of **5** by Swern's reagent [(COCl)₂ and DMSO] or DMSO and P₂O₅ produced the known aldehyde drimenal (**6**) in yields of 94 and 95%, respectively. We note that the method using P₂O₅ is more convenient because the reaction occurs at ambient temperature whereas oxidation by Swern's reagent occurs at -60°C. Aldehyde **6** was identified using spectral data, which were identical to those in the literature [8]. Previously drimenal (**6**) was prepared by oxidation of drimenol (**5**) by pyridinium chlorochromate (PCC) (75% yield) [8] or CrO₃ in pyridine (30% yield) [9]. In the latter instance, nordrimanic compounds are formed in addition to drimenal. According to the literature [10], the single product of drimenol oxidation by PCC is isonordrimenone (**7**) (71% yield). Thus, the reagents used by us to oxidize **5** to **6** were more effective and selective.

In the next step, **6** was isomerized into the known isodrimenal (**8**). The isomerizing reagents were MeONa, cation-exchanger Ku-23, and *p*-TsOH. The yield of isodrimenal according to GC was only 3.2% if MeONa in MeOH at ambient temperature was used. The principal reaction product was an unknown compound that was not investigated further. Boiling drimenal with cation-exchanger Ku-23 in hexane under an inert atmosphere for 1.5 h gave **8** in 64% yield. The best result was obtained by boiling **6** with *p*-TsOH in benzene under an inert atmosphere. The yield of **8** reached 79%. We note that **8** has been isolated from *Diplophyllum serrulatum* [11] and synthesized as an important intermediate in the preparation of certain valuable biologically active compounds isolated from marine sponges [12-14]. We identified **8** by comparing its spectral properties to those in the literature [13, 14].

Isodrimenal was reduced by NaBH₄ into isodrimenol (**9**), which was identified by comparing its physicochemical and spectral properties to those in the literature [13-15].

Reaction of **9** with *m*-chloroperbenzoic acid (*m*-CPBA) formed a liquid mixture of the known 8,9 α -(**10**) and 8,9 β -epoxydriman-11-ols (**11**) [7] in a 3.4:1 ratio (in 95.5% yield according to GC). The PMR spectrum of this mixture was readily interpreted as signals for protons belonging to the predominant **10**, which completely agreed with the literature [7]. Signals for protons of the minor product **11** could not be distinguished owing to their weakness. The mixture of **10** and **11** was used without separation in the next step. Its reaction with *p*-tosylchloride in Py gave in good yield a mixture of epoxytosylates **12** and **13**, which was characterized by spectroscopy. Subsequent reaction of **12** and **13** first with KI in an acetone:DMF mixture with heating and then with Ph₃P with cooling formed a mixture of drim-9(11)-en-8 α -ol (**3**) and drim-9(11)-en-8 β -ol (**4**) in a 2.5:1 ratio and in 60% yield. The mixture was separated by chromatography. Compounds **3** and **4** were identified by comparing their physicochemical and spectral properties with those in the literature [1, 5, 6].

Thus, drim-9(11)-en-8-ols **3** and **4** were synthesized in ~26% yield in six steps from drimenol (**5**).

EXPERIMENTAL

Melting points were determined on a Boetius stage. IR spectra were recorded on a Specord-74 spectrophotometer in CCl₄. PMR and ¹³C NMR spectra were recorded in CDCl₃ on Bruker AC-E200 (200 and 50 MHz) and Bruker AC-80 (80 and 20 MHz) spectrometers. Chemical shifts are given on the δ scale in parts per million relative to signals of CHCl₃ as an internal standard (at 7.24 and 77.00 ppm, respectively). Signals in ¹³C NMR spectra were assigned using the DEPT technique and comparison with spectra of known related compounds [3-6, 11-14]. Specific rotation was measured in CHCl₃ on a Perkin-Elmer 241 polarimeter. GC was performed on a Chrom-5 chromatograph [flame-ionization detector, CI-100A integrator, glass column 1200 \times 3 mm, Carbowax 20 M on Inerton AW-DMCS (0.16-0.20 mm), temperature programming from 90 to 200°C at 10°C/min, and He carrier gas]. The course of reactions was monitored by TLC on Silufol plates with development by I₂ vapor. Column chromatography used silica gel grade L (100/160 and 100/400 μ m) and neutral Al₂O₃ (Brockman activity III-IV). Solutions of compounds in organic solvents were dried over anhydrous MgSO₄. Elemental analyses of newly prepared compounds agreed with those calculated.

Oxidation of Drimenol (5). a. Swern's Reagent. A cooled (-60°C) solution of oxalylchloride (0.2 mL, 296 mg, 2.33 mmol) in CH₂Cl₂ (4.6 mL) was treated with a solution of dry DMSO (340 mg, 0.31 mL, 4.35 mmol) in CH₂Cl₂ (1.73 mL). The mixture was stirred for 5 min, treated with a solution of **5** (100 mg, 0.45 mmol) in CH₂Cl₂ (0.91 mL), stirred at the same temperature for 45 min, treated with Et₃N (1.1 g, 1.53 mL, 10.87 mmol), stirred for 10 min, warmed, and treated with water (12.7 mL) after 25 min. The mixture was extracted with ether (4 \times 20 mL). The extract was washed with NaHCO₃ solution (5%, 20 mL) and water (2 \times 20 mL), dried, and filtered. The solvent was removed in vacuo under a stream of N₂. The solid was dissolved in hexane (10 mL). The solution was passed over a column of SiO₂ (0.8 g). The column was washed with hexane (20 mL). The hexane was distilled in vacuum under a stream of N₂ to afford the pure (according to TLC and GC) liquid

compound (93 mg, 94% yield) that was **6** according to IR and PMR spectra. IR spectrum (ν , cm^{-1}): 840, 1665 ($>\text{C}=\text{C}<_{\text{H}}$), 1715, 2720 (CHO).

PMR spectrum (δ , ppm, J/Hz): 0.87 (s, 3H, CH_3 -13), 0.91 (s, 3H, CH_3 -14), 1.06 (s, 3H, CH_3 -15), 1.61 (br.s, 3H, CH_3 -12), 5.69 (m, 1H, H-7), 9.69 (d, 1H, J = 5, CHO). Compound **6** was identified by comparing the spectral properties with those in the literature [8].

b. P_2O_5 in DMSO. A solution of **5** (500 mg, 2.25 mmol) in CH_2Cl_2 (20 mL) was treated with stirring and cooling in an ice bath with dry DMSO (1 mL, 1.1 g, 14.08 mmol) and P_2O_5 (2 g, 14.09 mmol), held for 5 min, stirred at 15–17°C for 30 min, again cooled on ice, treated with Et_3N (1.2 mL, 0.86 g, 8.5 mmol), warmed, and stirred at 15–17°C for 30 min. The reaction mixture was cooled again, diluted with water (2.5 mL), acidified with HCl (2.5 mL, 5%), and extracted with CH_2Cl_2 (3×40 mL). The extract was washed with saturated NaCl solution (5×20 mL), dried, and filtered. Solvent was removed in vacuo under a stream of N_2 . The product was dissolved in hexane (30 mL) and passed over a column of SiO_2 (0.5 g). The column was washed with hexane (20 mL). The hexane was removed in vacuo under a stream of N_2 to afford the product (470 mg, 94.9% yield), the spectral properties of which were identical to those above (in part a).

Drimenal (6) Isomerization. A solution of **6** (300 mg, 1.36 mmol) in dry C_6H_6 (15 mL) was treated with *p*-TsOH (94 mg, 5.46 mmol), boiled under N_2 for 1 h, diluted with Et_2O (100 mL), washed with NaHCO_3 solution (5%, 2×20 mL) and NaCl solution (2×20 mL), dried, and filtered. The solvent was removed in vacuo under a stream of N_2 . The solid was chromatographed over a column of SiO_2 (6 g) with elution by hexane to afford liquid **8** (245 mg, 81.6% yield). IR spectrum (ν , cm^{-1}): 1674, 2740 (conjugated CHO), 1610 (conjugated $>\text{C}=\text{C}<$).

PMR spectrum (δ , ppm): 0.86 (s, 3H, CH_3 -13), 0.90 (s, 3H, CH_3 -14), 1.18 (s, 3H, CH_3 -15), 2.03 (s, 3H, CH_3 -8), 10.04 (s, 1H, H-11). The spectral data correspond with those in the literature for **8** [12–14].

Isodrimenal (8) Reduction. A solution of **8** (245 mg, 1.11 mmol) in EtOH (12 mL) was treated in portions over 5 min with stirring and cooling in an ice bath with NaBH_4 (220 mg, 5.81 mmol). Stirring was continued for another 20 min. The reaction mixture was treated dropwise over 20 min with water (12 mL) and HCl (5%, 4.8 mL). The mixture was extracted with ether (3×30 mL). The extract was washed with NaCl solution (3×20 mL), dried, and filtered. Solvent was removed in vacuum to afford a crystalline solid (242 mg) that was recrystallized from hexane to give **9** (185 mg, 75% yield), mp 117–118°C, $[\alpha]_{\text{D}}^{20} +100^\circ$ (*c* 0.65). IR spectrum (ν , cm^{-1}): 1030, 3450 (band), 3640 (OH).

PMR spectrum (δ , ppm, J/Hz): 0.85 (s, 3H, CH_3 -15), 0.89 (s, 3H, CH_3 -13), 0.97 (s, 3H, CH_3 -14), 1.72 (s, 3H, CH_3 -12), 2.05 (m, 2H, H₂-7), 4.04 and 4.20 (both d, 1H each, J = 11.5, AB-system, H₂-11).

^{13}C NMR spectrum (δ , ppm): 18.97 (C-2), 19.03 (C-6), 19.37 (C-15), 20.78 (C-13), 21.66 (C-12), 33.30 (C-14), 33.34 (C-4), 33.78 (C-7), 36.89 (C-1), 38.14 (C-10), 41.77 (C-3), 51.79 (C-5), 58.37 (C-11), 132.50 (C-8), 141.07 (C-9). The spectral properties correspond with those in the literature [13–15]. Lit. [14] mp 93–94°C, $[\alpha]_{\text{D}}^{20} +105.4^\circ$ [15].

Isodrimenol (9) Epoxidation. A solution of **9** (230 mg, 1.03 mmol) in CH_2Cl_2 (10 mL) was treated with stirring and cooling in an ice bath with *m*-CPBA (330 mg, 83%, 1.59 mmol). The mixture was stirred at the same temperature for another 2 h, diluted with water (23 mL), and extracted with ether (3×30 mL). The extract was washed with NaHCO_3 solution (5%, 20 mL) and water (2×20 mL), dried, and filtered. Solvent was removed in vacuo. The solid was dissolved in hexane (10 mL) and passed over a layer of SiO_2 (0.2 g). The SiO_2 was washed with hexane (10 mL). The hexane was removed in vacuo to afford a mixture of 8,9- α - (**10**) and 8,9- β -epoxydriman-11-ols (**11**) (235 mg, 95.5%) in a 3.4:1 ratio (GC).

IR spectrum (ν , cm^{-1}): 845, 1152 ($=\text{C}-\text{O}-\text{C}=$), 3400 (band) (OH).

The PMR spectrum of this mixture contains strong signals for the predominant 8,9- α -epoxyalcohol **10**, which were identical to those in the literature [7].

PMR spectrum (δ , ppm, J/Hz): 0.82 (s, 3H, CH_3 -13), 0.85 (s, 3H, CH_3 -14), 0.98 (s, 3H, CH_3 -15), 1.31 (s, 3H, CH_3 -12), 3.55 and 3.90 (both d, 1H each, J = 10.9, AB-system, H₂-11).

Signals for the β -epoxyalcohol **11** are difficult to find in the PMR spectrum of the mixture of **10** and **11** because of their weakness and superposition on signals of other protons.

Tosylation of the Mixture of 10 and 11. A solution of the mixture of **10** and **11** (235 mg, 0.98 mmol) in Py (9 mL) was treated with *p*-tosylchloride (520 mg, 2.73 mmol), stirred, left at room temperature for 48 h, acidified with H_2SO_4 (10%), and extracted with ether (5×30 mL). The extract was washed with water (20 mL), NaHCO_3 solution (5%, 20 mL), and water (2×20 mL), dried, and filtered. The solvent was removed in vacuo under a stream of N_2 . The solid was dissolved in hexane (15 mL). The solution was filtered through a layer of SiO_2 (0.3 g). The silica gel was washed with a hexane:ether (19:1)

mixture. The solvent was removed from the filtrate to afford a liquid mixture of tosylates of 8,9- α - and 8,9- β -epoxydriman-11-ols (**12** and **13**, 300 mg, 77.5% yield).

IR spectrum (film, ν , cm^{-1}): 749, 838, 914, 1255 (epoxy), 794, 813, 1086, 1097, 1290, 1459, 1598 (benzene ring), 1175, 1188, 1364 ($-\text{OSO}_2-$).

PMR spectrum of predominant **12** (δ , ppm, J/Hz): 0.74 (s, 3H, CH_3 -15), 0.79 (s, 3H, CH_3 -13), 1.06 (s, 3H, CH_3 -14), 1.17 (s, 3H, CH_3 -12), 2.45 (s, 3H, CH_3 - C_6H_4), 3.76 and 4.45 (both d, 1H each, $J = 10.4$, AB-system, H_2 -11), 7.35 and 7.78 (both d, 2H each, $J = 8.0$, two pairs of *o*-protons on the benzene ring).

Preparation of Drim-9(11)-en-8-ols 3 and 4. A solution of **12** and **13** (174 mg, 0.44 mmol) in dry acetone (9 mL) was treated with KI (0.6 g, 3.61 mmol) and dry DMF (2.8 mL), boiled for 3 h, cooled in an ice bath, stirred, treated with dry acetone (4 mL), Ph_3P (150 mg, 0.57 mmol), and I_2 crystals, stirred for another 1 h at the same temperature, and treated with ether (60 mL). The resulting solid was filtered off and washed with ether (20 mL). The filtrate was washed with $\text{Na}_2\text{S}_2\text{O}_3$ solution (2×10 mL), NaCl solution (2×10 mL), and water (2×10 mL), dried and filtered. Solvent was removed in vacuo. The solid was treated with hexane (10 mL), ground, and filtered. The solid on the filter was washed with hexane (3 mL). The hexane filtrate was partially evaporated and cooled. The resulting solid was filtered off and washed with hexane. The hexane was removed in vacuum. The solid was chromatographed over a column with Al_2O_3 (5 g). Hexane eluted first a mixture of β -epimer **4** (37 mg) with less polar products and then a mixture of **3** and **4** (19 mg) and nonpolar impurities; hexane:ether (49:1), pure **3** (35 mg), mp 49-50°C (hexane).

IR spectrum (ν , cm^{-1}): 900, 1630, 3120 ($>\text{C}=\text{CH}_2$), 1070, 3500 (band), 3620 (OH).

PMR spectrum (δ , ppm): 0.85 (s, 3H, CH_3 -13), 0.87 (s, 3H, CH_3 -14), 1.09 (s, 3H, CH_3 -15), 1.41 (s, 3H, CH_3 -12), 4.84 and 5.16 (both s, 1H each, H_2 -11). Lit. [2] mp 50-53°C. The spectral properties of **3** are identical to those in the literature [1, 5, 6]. It was also identified by direct comparison of spectra and chromatograms with those of an authentic sample prepared previously by us [5].

Preparative TLC on Silufol UV-254 of the first two chromatographic fractions (37 and 19 mg) (see above) using benzene:ether (3:1) isolated an additional portion of **3** (7 mg) and **4** (17 mg), mp 74-76°C (hexane).

IR spectrum (ν , cm^{-1}): 900, 1630, 3150 ($>\text{C}=\text{CH}_2$), 1070, 3400 (weak band), 3620 (OH).

PMR spectrum (δ , ppm): 0.87 (s, 3H, CH_3 -13), 0.89 (s, 3H, CH_3 -14), 1.25 (s, 3H, CH_3 -15), 1.38 (s, 3H, CH_3 -12), 4.87 and 5.04 (both s, 1H each, H_2 -11). Alcohol **4** was described in the literature as a liquid [6]. Its spectral properties are identical to those given for it [6] and its enantiomer [1]. The overall yield of **3** and **4** was 60% in a 2.5:1 ratio.

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