Synthesis of (+)-drim-9(11)-en-8α-ol from sclareol

P. F. Vlad, A. N. Aryku, and A. G. Chokyrlan*

Institute of Chemistry, Academy of Sciences of the Moldova Republic,
ul. Akademiei 3, MD-2028 Kishinev, the Republic of Moldova
Fax: +7 (373 2) 73 9775. E-mail: vlad_p@mail.md

A drimane-type sesquiterpenoid, (+)-drim-9(11)-en-8α-ol, was synthesized from sclareol in four steps. The ozonolysis product of sclareol diacetate reacts with $Cu(OAc)_2 \cdot H_2O$ to give 8α-acetoxy-14,15-bisnorlabdan-13-one. Photolysis of this compound followed by alkaline hydrolysis results in the target compound belonging to the normal steric series. (+)-Drim-9(11)-en-8α-ol acetate is highly unstable and decomposes during chromatography on SiO_2.

Key words: (+)-drim-9(11)-en-8α-ol, synthesis, ozonolysis, photolysis, absolute configuration, sclareol.

Sesquiterpenoid drimane-type alcohols, namely, (−)-drim-9(11)-en-8α-ol (**1**) and its dextrorotatory C(8)-epimer (**2**), were isolated[1] from the culture filtrate of the fungi *Aspergillus oryzae* used in breadmaking and in the production of some beverages (sake and so on) in Japan (Scheme 1). The racemic alcohol **1** was synthesized starting from farnesol, which ultimately confirmed its structure.

To establish the absolute configurations of compounds **1** and **2**, sesquiterpenes **3** and **4** were synthesized[2] from manool (**5**). Manool was converted in three steps into a mixture of C(8)-epimeric 14,15-bisnorlabdan-8-ol-13-ones **6** and **7**, whose photolytic cleavage produced a mixture of (+)-drim-9(11)-en-8α-ol (**3**) and (−)-drim-9(11)-en-8α-ol (**4**) and it was concluded that *A. oryzae* metabolites refer to the enantiomeric series. Later, a mixture of the same alcohols **3** and **4** was obtained[3] from royleanone (**8**), a natural product of the same stereochemical series as manool (**5**). However, these researchers concluded that the metabolites of *A. oryzae* correspond to the normal steric series. It was also found[2,3] that the specific optical rotation value reported previously[1] for alcohol **1** is markedly overestimated.

Enantioselective synthesis of crystalline alcohol **3** in which drimane-8α,11-diol (**9**) served as the key compound has been described.[3,4] The conclusions drawn are in keeping with those reported in a previous publication.[2]

In view of the above contradictory data, to solve definitely the problem of the absolute configuration of the metabolites of the fungi *A. oryzae*, we carried out directed partial synthesis of alcohol **3** from sclareol (**10**) (see Scheme 1).

8α-Acetoxy-14,15-bisnorlabdan-13-one (**11**) was chosen as the key intermediate compound, because 14,15-bisnorlabdan-8α-ol-13-one (**7**), formed upon oxidation of sclareol (**10**), is difficult to prepare in a pure state, as it is unstable and is easily converted into cyclic vinyl ether **12**.[5—7]

It is noteworthy that acetoxy ketone **11** is an important intermediate for the synthesis of products with amber odor valuable for the fragrance industry.[7—11] The development of methods for its preparation from sclareol (**10**) has received considerable attention. This compound was first synthesized[6] from hydroxy ketone **7** in a low yield (25—27%) by a complex, multistage route. It is also formed[12] upon $Pb(OAc)_4/I_2$- or $PhI(OAc)_2/I_2$-induced radical cleavage of dihydrosclareol 8-monoacetate (**13**). Acetoxy ketone **11** was obtained in a high yield (95%) upon oxidation of sclareol 8-monoacetate (**14**) on treatment with $RuCl_3 \cdot 3H_2O$ and $NaIO_4$ [9,10] (the overall yield based on sclareol (**10**) was 51%). However, the most efficient method for the preparation of acetoxy ketone **11** from sclareol (**10**) includes quantitative isomerization of sclareol diacetate (**15**) induced by the $PdCl_2 \cdot (MeCN)_2$ complex to give isosclareol diacetate (**16**)[8,10,13] and its oxidative ozonolysis (the yield of acetoxy ketone **11** was 90%)[8,10] or scission with $KMnO_4$ (85% yield).[10]

Of course, it would be of interest to accomplish direct oxidative transformation of sclareol diacetate (**15**) into acetoxy ketone **11**. To this end, we performed a detailed investigation of its reactions with oxidants such as $KMnO_4$, CrO_3, and O_3 under various conditions. Sclareol diacetate (**15**) was prepared by a known procedure.[14] The oxidation of diacetate **15** with $KMnO_4$ was carried out under standard conditions in acetone, acetic acid, acetone in the presence of $MgSO_4 \cdot 7H_2O$ (see Ref. 2), or in benzene in the presence of $CuSO_4 \cdot 5H_2O$ (see Ref. 15). However, under these conditions, acetoxy ketone **11** either formed in a yield of no more than 25—27% (in acetone and acetic acid) or was not formed at all. The oxidation of

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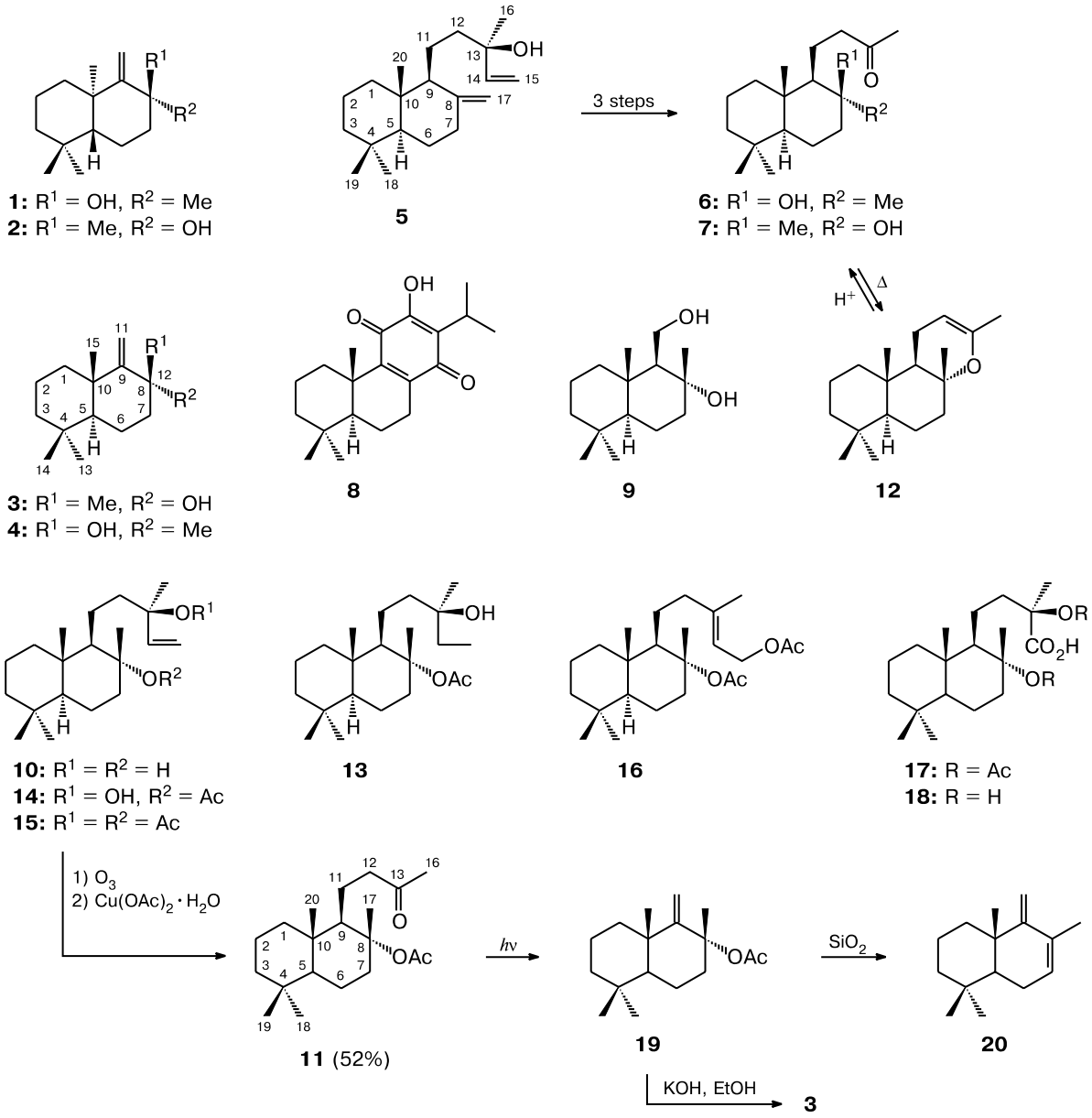
Scheme 1



diacetate **15** with the Jones reagent or CrO_3 in AcOH did not result in acetoxy ketone **11** either. Ozonolysis of diacetate **15** in CH_2Cl_2—Et_3N (see Ref. 16), MeOH—CH_2Cl_2—Py, or CH_2Cl_2 followed by oxidative cleavage of the ozonide with H_2O_2 gave acetoxy ketone **11** in a yield ranging from 10 to 17%. The desired compound was not formed at all upon ozonolysis of diacetate **15** in a MeOH—CH_2Cl_2 mixture in the presence of NaOH (see Ref. 17) or in MeOH in the presence of HCl (see Ref. 18). Better results were obtained by ozonization of diacetate **15** in a MeOH—CH_2Cl_2 mixture followed by anomalous decomposition of the resulting hydroperoxides by treatment with a mixture of $FeSO_4 \cdot 7H_2O$ and $Cu(OAc)_2 \cdot H_2O$ (see Ref. 19). The neutral fraction of the ozonolysis product was a mixture of the target acetoxy ketone **11** and a small amount of a more polar compound, which was not studied further. However, in this case, too, the yield of acetoxy ketone **11** proved to be relatively low (38%). A reasonable yield of acetoxy ketone **11** (52%) was obtained upon decomposition of the ozonolysis product of sclareol diacetate (**15**) by $Cu(OAc)_2 \cdot H_2O$ in toluene with heating, carried out according to a previously described procedure.[20] Compound **11** was identified by comparing the physicochemical and spectroscopic characteristics obtained with published data.[11]

The acidic fraction of the ozonization product is sclareolic acid diacetate (**17**) as indicated by the data from spectral and elemental analysis and was confirmed by the preparation of the known sclareolic acid (**18**)[5] by saponification of the product by ethanolic alkali.

For preparing 8α-acetoxydrim-9(11)-ene (**19**), acetoxy ketone **11** was subjected to photolytic cleavage according to the Norrish II reaction. Note that this reaction has been studied previously,[21] and a diene, drim-7,9(11)-diene (**20**), has been isolated as the only reaction product. In view of the mechanism and mild conditions of the Norrish II reaction, this result was difficult to explain and we suggested that the primary reaction product, unsaturated acetate **19**, decomposes during chromatography, as tertiary alcohol acetates are known to be highly labile compounds.[22] Indeed, by photolysis of acetoxy ketone **11**, we obtained a mixture of the starting compound (the reaction did not proceed to completion) and a less polar compound; during chromatography on a SiO_2 column, the latter compound was quantitatively transformed into another product with even a lower polarity, which was found to be diene **20**. The obtained spectroscopic characteristics were fully consistent with published data.[21] Alcohol **3** was also found to decompose during chromatography on silica gel Acros. This fact was confirmed experimentally: the photolysis product was hydrolyzed with an ethanolic solution of alkali; the mixture of alcohol **3** and sclareol oxide (**12**) was separated into two portions, one of which was chromatographed on a column with SiO_2 and the other, on a column with neutral Al_2O_3. On the SiO_2 column, alcohol **3** dehydrated to give hydrocarbon **20**. Chromatography on Al_2O_3 gave the crystalline target product **3** and sclareol oxide (**12**), which was identified by comparison with an authentic sample. The melting point of alcohol **3** coincided with the reported value[4] and the spectral characteristics were also identical to those reported in the literature.[1,2]

Thus, we accomplished a four-step synthesis of (+)-drim-9(11)-en-8α-ol (**3**) from sclareol (**10**) in an overall yield of 45% (taking into account the recovered acetoxy ketone **11** at the stage of photolysis), which additionally proves the fact that natural products **1** and **2** belong to the enantiomeric steric series.

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 run in $CDCl_3$ on a Bruker AC-E 200 spectrometer (200.13 and 50.32 MHz). The chemical shifts are given in the δ scale and referred to $CHCl_3$ as the internal standard (δ_H 7.24, δ_C 77.00). The ^{13}C NMR signals were assigned using DEPT technique and comparison with the spectra of known related compounds. Mass spectra (EI, 70 eV) were run on a AEI MS 902 mass spectrometer. The specific rotation was measured on a JASCO DIP 370 polarimeter in $CHCl_3$. Photolysis was performed using a Heraeus TQ-150 UV lamp, 150 W (a high-pressure mercury lamp). Acros silica gel (60/200 μm) was used for column chromatography and Sorbfil plates were used for TLC (visualization by H_2SO_4 with heating).

Ozonolysis of sclareol diacetate (15). *A*. A flow of ozonized oxygen was passed at −60 °C through a solution of 100 mg (0.255 mmol) of sclareol diacetate (**15**)[14] in a mixture of 3 mL of anhydrous MeOH and 3 mL of dry CH_2Cl_2 until a persistent blue color appeared. Excess ozone was removed by purging the solution with nitrogen. Then the reaction mixture was warmed to ≈20 °C and the solvent was evaporated *in vacuo*. A solution of $Cu(OAc)_2 \cdot H_2O$ (51 mg, 0.255 mmol) in 5 mL of methanol was added to the residue, and $FeSO_4 \cdot 7H_2O$ (71 mg, 0.255 mmol) was added to the resulting solution (see Ref. 19). The mixture was stirred for 40 h at ~20 °C, diluted with 20 mL of ethyl acetate, washed successively with 1% HCl (2×20 mL) and water (2×20 mL), and extracted with 1% NaOH (2×20 mL). The organic layer was washed with water (3×20 mL), dried with anhydrous Na_2SO_4, and filtered, and the solvent was evaporated *in vacuo*. The resulting neutral fraction (53 mg) was chromatographed on a column with 1.6 g of SiO_2. Elution with a petroleum ether—Et_2O mixture (98 : 2) gave 32 mg (yield 38%) of 8α-acetoxy-14,15-bisnorlabdan-13-one (**11**), m.p. 119—120 °C (from a hexane—Et_2O mixture, 98 : 2), $[\alpha]_D^{22}$ −26.5 (*c* 2.17) (Ref. 11: m.p. 118—121 °C, $[\alpha]_D$ −22.2). IR, ν/cm^{-1}: 1245, 1735 (OAc), 1700 (COMe). ^1H NMR, δ: 0.77 (s, 3 H, C(20)H_3); 0.83 and 0.85 (both s, 3 H each, C(4)(CH_3)$_2$); 1.46 (s, 3 H, C(17)H_3); 1.92 (s, 3 H, OAc); 2.12 (s, 3 H, C(16)H_3).

The alkaline extract from the ozonolysis product was acidified with 15 mL of 10% H_2SO_4 and extracted with ether (3×20 mL), the extract was washed with water to neutral pH, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give 26 mg (24.9%) of sclareolic acid diacetate **17**, m.p. 83—85 °C (from a hexane—Et_2O mixture, 96 : 4). Found (%): C, 67.5; H, 8.97. $C_{23}H_{38}O_6$. Calculated (%): C, 67.29; H, 9.33. IR, ν/cm^{-1}: 1230, 1725 (OAc), 1710, 3340 (COOH). ^1H NMR, δ: 0.78 (s, 3 H, C(20)H_3); 0.84 (s, 3 H, C(18)H_3); 0.86 (s, 3 H, C(19)H_3); 1.42 (s, 3 H, C(17)H_3); 1.60 (s, 3 H, C(16)H_3); 1.93, 2.07 (both s, 3 H each, OAc).

B. Sclareol diacetate (**15**) (100 mg, 0.255 mmol) was ozonized as described above. After evaporation of the solvent *in vacuo*, the residue was dissolved in 2 mL of toluene, and the resulting solution was added to a solution of $Cu(OAc)_2 \cdot H_2O$ (102 mg, 0.51 mmol) in 5 mL of methanol heated to 70 °C. The mixture was stirred at the same temperature for 20 h and filtered. Ether (20 mL) was added to the filtrate and the solution was washed with 1% NaOH (2×20 mL) and H_2O (3×20 mL). The solution was dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue (57 mg) was chromatographed on a column with 15 g of SiO_2 to give 43 mg (52%) of acetoxy ketone **11**, m.p. 119—120.5 °C (from a hexane—Et_2O mixture, 98 : 2) and 4 mg of a more polar compound, which was not further studied. The yield of sclareolic acid diacetate (**17**) was 16 mg (15.3%).

Saponification of sclareolic acid diacetate (17). Sclareolic acid diacetate (**17**) (70 mg, 0.169 mmol) was refluxed for 3 h with 5 mL of 10% KOH in ethanol. Ethanol was evaporated *in vacuo*, the residue was dissolved in 20 mL of ether, and the ethereal solution was washed with water to neutral pH (4×10 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give 45 mg (80.8%) of sclareolic acid (**18**),

m.p. 152—153 °C (from a hexane—Et_2O mixture, 96 : 4), which was identified by comparison with an authentic sample (Ref. 5: m.p. 153—154 °C).

Photolysis of 8α-acetoxy-14,15-bisnorlabdan-13-one (11). *A*. A solution (110 mg, 0.34 mmol) of acetoxy ketone **11** in 60 mL of anhydrous hexane was irradiated in a Pyrex vessel with a Heraeus TQ-150 UV lamp (150 W) under a flow of dry nitrogen for 2 h at 5 °C. The solvent was evaporated *in vacuo* and the residue representing, according to TLC, a mixture of the starting compound and a less polar product was chromatographed on a column with 11 g of SiO_2. Elution with light petroleum gave 32 mg of a low-polar liquid differing from the compound applied onto the column (TLC data), and elution with a light petroleum—Et_2O mixture (98 : 2) afforded 59 mg of the starting acetoxy ketone **11**. According to spectral data, the low-polar product represented known[21] drim-7,9(11)-diene (**20**) (the yield with allowance for the recovered acetoxy ketone **11** was 99%). IR, ν/cm^{-1}: 821, 3103 (>C=C<$_H$), 884 (>C=CH_2), 1651 (conjugated double bonds). ^{1}H NMR, δ: 0.76 (s, 3 H, C(15)H_3); 0.81 (s, 3 H, C(13)H_3); 0.85 (s, 3 H, C(14)H_3); 1.72 (s, 3 H, C(12)H_3); 4.72, 4.76 (both s, 1 H each, C(11)H_2); 5.59 (br.s, C(7)H). ^{13}C NMR, δ: 19.06 (C(2)); 20.61 (C(15)); 21.11 (C(13)); 22.16 (C(12)); 24.29 (C(6)); 32.94 (C(14)); 33.37 (C(4)); 37.69 (C(1)); 37.78 (C(10)); 42.16 (C(3)); 48.64 (C(5)); 103.75 (C(11)); 126.52 (C(7)); 131.19 (C(8)); 158.17 (C(9)).

B. Acetoxy ketone **11** (85 mg, 0.264 mmol) was subjected to photolysis under conditions described above and the product was refluxed with a solution of KOH (79 mg, 1.4 mmol) in 10 mL of ethanol for 3 h. Ethanol was evaporated *in vacuo*, the residue was extracted with ether (10 mL), the extract was washed with water (3×10 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The reaction product consisting, according to TLC, of a nonpolar compound and sclareol oxide (**12**) was separated into two portions. The first portion (20 mg) was chromatographed on a column with 4 g of SiO_2. The product was eluted with light petroleum, which gave 13 mg of diene **20**.

The second portion of the hydrolysis product (45 mg) was chromatographed on a column with 0.9 g of neutral Al_2O_3 (activity III). Elution by light petroleum gave 18 mg (43.9%) of drim-9(11)-en-8α-ol (**3**), m.p. 50—51 °C (from hexane), $[\alpha]_D^{23}$ +15.2 (*c* 0.45) (Ref. 4: m.p. 52—53 °C, $[\alpha]_D$ +28.6 (*c* 0.28, $CHCl_3$)). IR (film), ν/cm^{-1}: 907, 1630, 3102 (>C=CH_2), 1074, 3403 (band) (OH). ^{1}H NMR, δ: 0.77 (s, 3 H, C(15)H_3); 0.80 (s, 3 H, C(13)H_3); 1.02 (s, 3 H, C(14)H_3); 1.34 (s, 3 H, C(12)H_3); 4.77, 5.15 (both s, 1 H each, C(11)H_2). ^{13}C NMR, δ: 19.06 (C(2)); 20.20 (C(6)); 21.63 (C(15)); 22.40 (C(14)); 30.52 (C(12)); 33.26 (C(13)); 33.80 (C(4)); 39.01 (C(1)); 40.03 (C(10)); 41.77 (C(3)); 44.20 (C(7)); 53.48 (C(5)); 73.38 (C(8)); 103.66 (C(11)); 166.64 (C(9)). MS, *m/z* (I_{rel} (%)): 222 $[M]^+$ (4.5), 204 $[M - H_2O]^+$ (100), 189 $[M - H_2O - Me]^+$ (84), 161 $[M - H_2O - Me - C_2H_4]^+$ (30); ion peaks typical of the bicyclic system of labdane diterpenoids were also present,[23] *m/z* 135 (27), 133 (27), 119 (28), 109 (28), 108 (27), 95 (37), 43 (34).

Further elution with a mixture of light petroleum and Et_2O (99 : 1) gave **19** mg of sclareol oxide (**12**), which was identified by comparison with an authentic sample.

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