Synthesis of 11-hydroxydrim-8(9)-en-7-one and 11,12-dihydroxydrim-8(9)-en-7-one from drim-8(9)-en-7-one

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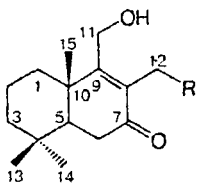
A synthetic route to 11-hydroxydrim-8(9)-en-7-one and 11,12-hydroxydrim-8(9)-en-7-one, valuable key intermediates for the preparation of naturally occurring biologically active drimanic sesquiterpenoids, starting from easily available drim-8(9)-en-7-one was developed. 11-Hydroxydrim-8(9)-en-7-one was obtained by peracidic oxidation of the enol acetate of drim-8(9)-en-7-one. 11,12-Dihydroxydrim-8(9)-en-7-one was synthesized from drim-8(9)-en-7-one by two routes, namely, by a five-step procedure *via* 11-hydroxydrim-8(9)-en-7-one and by bromination of drim-8(9)-en-7-one with NBS to give 11,12-dibromodrim-8(9)-en-7-one followed by its acetoxylation and deacetylation.

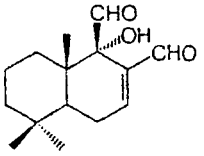
Key words: drimanic sesquiterpenoids, synthesis, drim-8(9)-en-7-one, 11-hydroxydrim-8(9)-en-7-one, 11,12-dihydroxydrim-8(9)-en-7-one.

(+)-11-Hydroxydrim-8(9)-en-7-one (**1**)[1,2] and 11,12-dihydroxydrim-8(9)-en-7-one (**2**)[3,4] are valuable synthons for the synthesis of natural biologically active polyfunctional drimane sesquiterpenoids. In particular, dihydroxy ketone **2** serves as the intermediate compound in the synthesis of highly reactive antifeedant warburganal (**3**).[5,6]

Recently,[7] we developed a convenient method for the synthesis of drim-8(9)-en-7-one (**4**) from norambreinolide (**5**) and thus it became a relatively easily available compound. In view of this fact, we attempted to prepare compounds **1** and **2** from ketone **4**; this was the purpose of the present study.



1: R = H
2: R = OH



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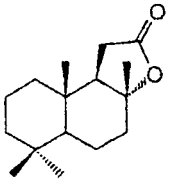

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Our approach to the directed introduction of a hydroxy group into the C(11) position of drim-8(9)-en-7-one (**4**) was based on the results obtained in a study of its enol acetylation. According to spectral data, the enol acetate of ketone **4** has a structure of 7-acetoxydrim-7,9(11)-diene (**6**), *i.e.*, the system of conjugated double bonds in this molecule is not homoannular but occupies the C(7)—C(8) and C(9)—C(11) positions. This is indicated by the maximum at 870 cm^{-1} in its IR spectrum, typical of a semicyclic double bond, and a two-proton signal in the vinylic region of the ^1H NMR spectrum.

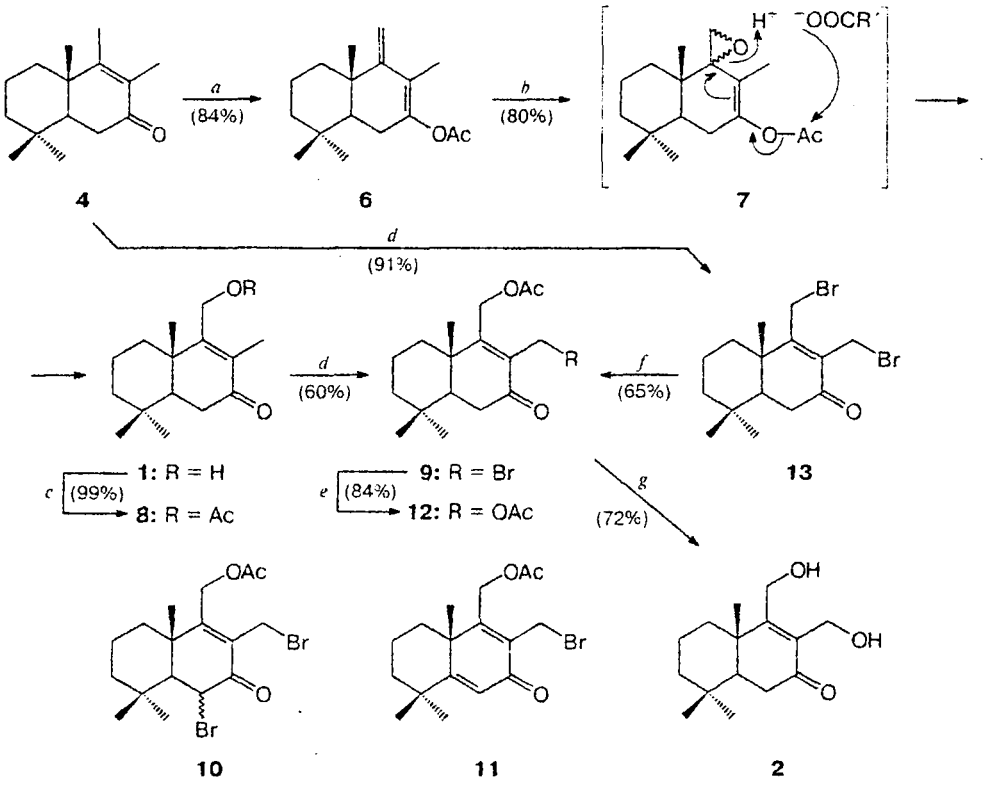
It should be noted that enol acetylation of ketone **4** with Ac_2O catalyzed by 72% $HClO_4$ or TsOH and carried out under standard conditions gives enol acetate **6** in a yield not higher than 20—25%, while unreacted drimenone **4** is recovered almost quantitatively. Numerous attempts to increase the yield of enol acetate **6** by varying the amount of the catalyst, the reaction temperature and time, or the order of mixing the reactants or by conducting the reaction in the presence of SiO_2 or molecular sieves failed. However, it was found that kinetically controlled enol acetylation of ketone **4** by isopropenyl acetate in the presence of TsOH (Scheme 1) is much more effective. The reaction was carried out in excess isopropenyl acetate or in dry benzene. In both cases, the yield of enol acetate **6** was higher than 80%; when isopropenyl acetate was used as the solvent, the reaction time was much shorter and the product yield was higher than in benzene.

In order to introduce a hydroxy group to the C(11) atom, enol acetate **6** was oxidized by excess monoperphthalic acid under mild conditions (4 °C). Although this afforded a mixture of four products, the reaction was highly selective and the yield of the major substance reached 79.5%. According to IR, ^1H NMR, and ^{13}C NMR spectroscopy and elemental analysis, this substance was not the expected epoxy acetate **7** but the product of its further acid-catalyzed isomerization, 11-hydroxydrim-8(9)-en-7-one (**1**) (see Scheme 1). (Hereinafter, the signals in the ^{13}C NMR spectrum were

†Deceased.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 1, pp. 95—98, January, 2000.

Scheme 1



Reagents and conditions: *a*. ⩾OAc /TsOH, Δ, 4 h. *b*. *o*-$C_6H_4(CO_2H)CO_3H$ (4.2 equiv), Et_2O, 4 °C, 48 h. *c*. Ac_2O/Py, 20 °C, 24 h. *d*. NBS/$CaCO_3$, CCl_4, Δ. *e*. AcOK/DMSO, 20 °C, 1 h. *f*. AcOK/DMF, 20 °C, 1 h. *g*. K_2CO_3, MeOH, 25 °C, 3 h.

assigned using a DEPT experiment and by comparison with published data for related drimane sesquiterpenes[8–11].)

The attempts to perform further functionalization of hydroxy ketone **1** at the C(12) atom by treatment with SeO_2 or NBS were unsuccessful; the reactions gave complex mixtures of products having no predominant components. Oxidation of the corresponding acetate, 11-acetoxydrim-8(9)-en-7-one (**8**), on treatment with SeO_2 led to similar results. Bromination of compound **8** with NBS occurs more unambiguously to give the expected 11-acetoxy-12-bromodrim-8(9)-en-7-one (**9**) as the major reaction product, as follows from spectral data (see Experimental). The minor reaction products have not been studied but, judging from spectral data, they are unstable epimeric dibromides **10** and bromodiene **11**. Thus, there is full analogy between bromination of acetoxy ketone **8** and drim-8(9)-en-7-one **4**. Compound **9** is smoothly acetoxylated on treatment with AcOK in DMSO to give the known 11,12-diacetoxydrim-8(9)-en-7-one (**12**), which serves as an intermediate[4] in the synthesis of warburganal **3**. The total yield of diacetoxy ketone **12** based on drimenone **4** (over five steps) was 28%. Diacetoxy ketone **12** can also be prepared from drimenone **4** using a shorter and more efficient two-step procedure in a total yield of 59% *via* a known product of bromination of drimenone **4** by NBS, 11,12-dibromodrim-8(9)-en-7-one (**13**).[7] Treatment of dibromide **13** with a solution of AcOK in DMF affords diacetoxy ketone **12**, whose deacetylation gives the previously unknown optically active crystalline 11,12-dihydroxydrim-8(9)-en-7-one (**2**) (see Scheme 1). The spectral characteristics of this product coincide with those reported[3] for its racemic form.

It should be noted that diacetoxy ketone **12** had been described as a crystalline compound.[4] However, our attempts to induce crystallization of this product failed. Therefore, to identify ketone **12** unambiguously, the deacetylation product, dihydroxy ketone **2**, was characterized not only by spectroscopy but also by X-ray diffraction analysis.[12]

Experimental

Melting points were determined on a Boetius hot stage. Specific rotation was determined on a JASCO DIP 370 instrument in $CHCl_3$. IR spectra were recorded on a Specord-74 spectrophotometer in CCl_4. ^1H and ^{13}C NMR spectra were

run in $CDCl_3$ on Varian-200 (200.13 and 50.32 MHz) and Bruker AM-400 spectrometers (400.13 and 100.13 MHz) using Me_4Si as the internal standard. Partial NMR spectra are presented; the signals of the protons of ring *A* are omitted. Column chromatography was performed using silica gel L (40/100 and 100/160 μm) and Across (60/200 μm). Plates with a fixed layer of SiO_2 LS (5/40 μm) containing 13% gypsum were used for TLC.

Enol acetylation of drim-8(9)-en-7-one (4). ***A.*** A mixture consisting of 40 mL of AcOEt, 4.1 mL of freshly distilled Ac_2O, and 8.5 mL of 72% $HClO_4$ was added with simultaneous bubbling of argon to a solution of drimenone **4** (0.5 g, 2.27 mmol) in 2.5 mL of AcOEt. The resulting mixture was kept at 17 °C for 1 h with stirring by bubbling argon and poured into a saturated solution of $NaHCO_3$ (50 mL). Crystalline $NaHCO_3$ was added in small portions over a period of 1 h until evolution of CO_2 ceased (~6 g $NaHCO_3$). The aqueous layer was separated and extracted with AcOEt (5×3 mL). The combined ethyl acetate extracts were washed twice with water and dried with Na_2SO_4 and the solvent was evaporated *in vacuo*. According to TLC, the liquid residue (0.52 g) consisted of the initial drimenone, a less polar product, and traces of two other compounds. This mixture was chromatographed on a column with 13 g of SiO_2. Elution with benzene gave 143 mg (24%) of 7-acetoxydrim-7,9(11)-diene (**6**) as a colorless liquid. Found (%): C, 77.92; H, 10.12. $C_{17}H_{26}O_2$. Calculated (%): C, 77.81; H, 9.99. IR (film), ν/cm^{-1}: 870, 3090 (>C=CH$_2$); 1600, 1660 (conjugated C=C bonds); 1210, 1744 (OAc). ^{1}H NMR (200.13 MHz), δ: 0.81 (s, 3 H, C(15)H$_3$); 0.86 (s, 3 H, C(13)H$_3$); 0.95 (s, 3 H, C(14)H$_3$); 1.53 (s, 3 H, C(12)H$_3$); 2.03 (s, 3 H, OAc); 4.73 (s, 2 H, C(11)H$_2$). Further elution with the same solvent gave 0.34 g (68%) of the starting drimenone **4**.

When enol acetylation was carried out in the presence of an equimolar amount of $HClO_4$ or when the reactants were mixed in reversed order, the yield of enol acetate **6** did not change.

B. Drimenone **4** (220 mg, 1 mmol) was dissolved in 10 mL of anhydrous ether; Ac_2O (0.3 mL, 312 mg, 3 mmol) and $TsOH \cdot H_2O$ (10 mg) were added and the mixture was refluxed for 30 h, washed with a saturated solution of $NaHCO_3$ (3×30 mL) and water, dried with Na_2SO_4, and concentrated *in vacuo*. The residue (240 mg) was chromatographed on a column with 8 g of SiO_2. Elution with a 3 : 1 petroleum ether—benzene mixture gave 50 mg (19%) of enol acetate **6**, and elution with a 3 : 1 benzene—AcOEt mixture afforded 180 mg (81%) of the initial drimenone **4**.

C. Drimenone **4** (110 mg, 0.5 mmol) was dissolved in 1 mL of isopropenyl acetate (Aldrich), $TsOH \cdot H_2O$ (4 mg) was added, and the solution was refluxed for 4 h until the reaction was completed (TLC monitoring). After cooling, 15 mL of ether was added, the solution was washed with 2 mL of a saturated solution of $NaHCO_3$ and water, and the organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The residue (150 mg) was chromatographed on a column with 5 g of SiO_2. Elution with a 3 : 1 petroleum ether—benzene mixture gave 110 mg (84%) of enol acetate **6**.

D. Isopropenyl acetate (1 mL) and $TsOH \cdot H_2O$ (8 mg) were added to a solution of drimenone **4** (350 mg) in 5 mL of anhydrous benzene and the solution was refluxed for 13 h. Then isopropenyl acetate (0.1 mL) and $TsOH \cdot H_2O$ (2 mg) were added and the mixture was refluxed for an additional 4 h. The solvent was evaporated *in vacuo* and the residue was dissolved in 15 mL of ether. The subsequent workup (see above) gave 310 mg (yield 82%) of enol acetate **6** and 60 mg (17%) of the initial drimenone **4**.

Oxidation of enol acetate 6 by monoperoxophthalic acid. A solution of monoperoxophthalic acid[13] (0.77 g, 4.25 mmol) in 10 mL of Et_2O cooled to 4 °C was added to enol acetate **6** (0.48 g, 1.83 mmol). The solution was kept at 4 °C for 48 h; the course of the reaction was monitored by TLC. The precipitate of phthalic acid was separated and washed with ether (3×5 mL). The combined ethereal extract was washed with a solution of $NaHCO_3$ and water, dried with Na_2SO_4, and concentrated *in vacuo*. The crystalline precipitate (0.56 g) (according to TLC, a mixture of four substances, in which the most polar product substantially predominated) was chromatographed on a column with 16 g of SiO_2. Elution with benzene gave 7.5 mg of a nonpolar fraction, and elution with a 9 : 1 benzene—AcOEt mixture gave two more small fractions (50 and 37 mg), which have not been studied. Elution with a 4 : 1 benzene—AcOEt mixture yielded 343 mg (79.5%) of 11-hydroxydrim-8(9)-en-7-one (**1**), m.p. 82—83 °C (from hexane), $[\alpha]_D^{20}$ +41° (*c* 0.55). Found (%): C, 76.76; H, 10.56. $C_{15}H_{24}O_2$. Calculated (%): C, 76.23; H, 10.24. IR (mineral oil), ν/cm^{-1}: 983, 3427 (br, OH); 1608 (conjugated C=C); 1651, 1670 (conjugated C=O). ^{1}H NMR (400.13 MHz), δ: 0.88 (s, 3 H, C(15)H$_3$); 0.92 (s, 3 H, C(13)H$_3$); 0.94 (s, 3 H, C(14)H$_3$); 1.86 (s, 3 H, C(12)H$_3$); 2.39 (dd, 1 H, C(6)H$_a$, J = 14.3, 17.6 Hz); 2.52 (dd, 1 H, C(6)H$_e$, J = 3.7, 17.6 Hz); 4.31, 4.37 (each 1 H, AB system, C(11)H$_2$, J = 11.6 Hz). ^{13}C NMR (100.13 MHz), δ: 11.29 (C(12)); 18.37 (C(15)); 18.48 (C(2)); 21.16 (C(14)); 32.48 (C(13)); 33.03 (C(4)); 35.27 (C(1) or C(6)); 35.52 (C(6) or C(1)); 39.95 (C(10)); 41.17 (C(3)); 50.23 (C(5)); 58.51 (C(11)); 132.40 (C(8)); 162.86 (C(9)); 201.13 (C(7)).

Acetylation of 11-hydroxydrim-8(9)-en-7-one (1). Acetic anhydride (2.5 mL, 26.52 mmol) was added to a solution of hydroxy ketone **1** (343 mg, 1.45 mmol) in 2.5 mL of anhydrous pyridine. The mixture was kept for 24 h at 20 °C until the reaction was complete (TLC monitoring), poured into water, and extracted three times with ether. The combined ethereal extract was washed with 10% H_2SO_4, water, a saturated solution of $NaHCO_3$, and water, dried with anhydrous Na_2SO_4, and filtered. The ether was evaporated *in vacuo* to give 400 mg (97%) of 11-acetoxydrim-8(9)-en-7-one (**8**), m.p. 63—64 °C (from hexane), $[\alpha]_D^{20}$ +86.2° (*c* 0.07). Lit. data: m.p. 61—62 °C,[2] $[\alpha]_D^{20}$ +60.6° (*c* 0.3).[1] IR (mineral oil), ν/cm^{-1}: 1223, 1740 (AcO); 1672 (conjugated >C=O). ^{1}H NMR (400.13 MHz), δ: 0.88 (s, 3 H, C(15)H$_3$); 0.91 (s, 3 H, C(13)H$_3$); 0.95 (s, 3 H, C(14)H$_3$); 1.79 (s, 3 H, C(12)H$_3$); 2.08 (s, 3 H, OAc); 2.40 (dd, 1 H, C(6)H$_a$, J = 14.0 and 17.6 Hz); 2.53 (dd, 1 H, C(6)H$_e$, J = 3.7 and 17.6 Hz); 4.70, 4.78 (each 1 H, AB system, C(11)H$_2$, J = 11.9 Hz). ^{13}C NMR (100.13 MHz), δ: 11.44 (C(12)); 18.27 (C(15)); 18.44 (C(2)); 20.84 (Me from OAc); 21.16 (C(14)); 32.46 (C(13)); 33.02 (C(4)); 35.27 (C(1) or C(6)); 35.33 (C(6) or C(1)); 39.40 (C(10)); 41.08 (C(3)); 50.10 (C(5)); 60.01 (C(11)); 134.53 (C(8)); 158.19 (C(9)); 170.65 (CH$_3$<u>C</u>O); 200.40 (C(7)).

Bromination of 11-acetoxydrim-8(9)-en-7-one (8). Freshly recrystallized NBS (114 mg, 0.64 mmol), $CaCO_3$ (70 mg, 0.7 mmol), and freshly precipitated benzoyl peroxide (6 mg) were added to a solution of acetoxy ketone **8** (0.15 g, 0.54 mmol) in 7 mL of anhydrous CCl_4. The mixture was refluxed for 30 min with irradiation by a incandescent lamp (100 W) and cooled. The precipitated succinimide was filtered off and washed with CCl_4, the filtrate was concentrated *in vacuo*, and the residue (0.24 g, a thick brown liquid) was chromatographed on a column with 6 g of SiO_2. Elution with benzene gave 52 mg of an unstable product; judging from spectral data, this was a mixture of two products. Subsequent elution gave 116 mg (yield 60%) of 11-acetoxy-12-bromodrim-8(9)-en-7-one (**9**),

m.p. 74.5—75.5 °C (from hexane), $[\alpha]_D^{20}$ +49.6° (*c* 0.28). Found (%): C, 57.23; H, 6.86; Br, 23.33. $C_{17}H_{25}BrO_3$. Calculated (%): C, 57.15; H, 7.00; Br, 22.38. IR, ν/cm^{-1}: 597, 1030 (Br); 1240, 1760 (OAc); 1608 (conjugated C=C); 1600 (conjugated >C=O). ^{1}H NMR (400.13 MHz), δ: 0.90 (s, 3 H, C(13)H_3); 0.93 (s, 3 H, C(14)H_3); 1.15 (s, 3 H, C(15)H_3); 2.11 (s, 3 H, OAc); 2.44 (dd, 1 H, C(6)H_a, *J* = 14.3 and 17.6 Hz); 2.60 (dd, 1 H, C(6)H_e, *J* = 3.7 and 17.6 Hz); 4.18, 4.29 (each 1 H, AB system, C(12)H_2, *J* = 9.9 Hz); 4.83, 4.89 (each 1 H, AB system, C(11)H_2, *J* = 12.5 Hz). ^{13}C NMR (100.13 MHz), δ: 18.13 (C(2)); 18.29 (C(15)); 20.90 (OAc); 21.19 (C(14)); 22.88 (C(12)); 32.37 (C(13)); 32.48 (C(4)); 34.70 (C(6) or C(1)); 35.16 (C(1) or C(6)); 40.50 (C(10)); 40.84 (C(3)); 49.63 (C(5)); 59.00 (C(11)); 135.21 (C(8)); 162.56 (C(9)); 170.29 (Me<u>C</u>O); 197.48 (C(7)). Further elution from the column by the same solvent yielded 16 mg of an unidentified substance.

Acetoxylation of 11-acetoxy-12-bromodrim-8(9)-en-7-one (9). Potassium acetate (110 mg, 1.12 mmol) was added to a solution of bromide **9** (200 mg, 0.56 mmol) in 3.5 mL of DMSO and the mixture was stirred for 1 h at 20 °C. Water (20 mL) was added and the product was extracted with ether (3×5 mL). The extract was washed twice with water, dried with Na_2SO_4, and concentrated *in vacuo*. The residue (210 mg) was chromatographed on a column with 8.4 g of SiO_2. Elution with a 98 : 2 benzene—AcOEt mixture afforded 10 mg of starting bromide **9** and then 150 mg (84%) of 11,12-diacetoxydrim-8(9)-en-7-one (**12**) as a colorless liquid, $[\alpha]_D^{20}$ +66.6° (*c* 1.38). IR, ν/cm^{-1}: 1240, 1750 (OAc); 1615 (conjugated C=C); 1670 (conjugated >C=O). ^{1}H NMR (200.13 MHz), δ: 0.90 (s, 3 H, C(13)H_3); 0.93 (s, 3 H, C(14)H_3); 1.17 (s, 3 H, C(15)H_3); 2.01 (s, 3 H, OAc); 2.05 (s, 3 H, OAc); 2.42 (dd, 1 H, C(6)H_a, *J* = 13.7 and 17.6 Hz); 2.59 (dd, 1 H, C(6)H_e, *J* = 4.3 and 17.6 Hz); 4.77, 4.87 (both d, each 2 H, two overlapping AB systems, C(11)H_2 and C(12)H_2, *J* = 12.5 Hz). Lit. data[4]: m.p. 87—88 °C, $[\alpha]_D^{20}$ +62.3°.

Acetoxylation of 11,12-dibromodrim-8(9)-en-7-one (13). Potassium acetate (150 mg, 1.58 mmol) was added to a solution of ketone **13** (300 mg, 0.79 mmol) in 5 mL of DMF. The mixture was stirred for 1 h at 20 °C, diluted with 20 mL of water, and extracted with ether (3×15 mL). The ethereal extracts were combined, washed with water, dried with Na_2SO_4, and concentrated *in vacuo*. The residue (290 mg) contained (TLC) four components; the most polar component, whose R_f value coincided with that of diacetate **12**, substantially predominated. The mixture of products was chromatographed on a column with 5.8 g of SiO_2 using gradient elution with a benzene—AcOEt mixture (95 : 5 → 90 : 10). This gave initially a mixture of the minor components (77 mg), which was not studied, and then 173 mg (65%) of diacetate **12**, whose chromatographic and spectral characteristics were identical to those of the product prepared previously from acetoxy bromide **9**.

Deacylation of 11,12-diacetoxydrim-8(9)-en-7-one (12). A 1% solution of K_2CO_3 (2 mL) in MeOH was added to a solution of diacetate **12** (50 mg, 0.15 mmol) in 0.5 mL of MeOH and the mixture was kept for 3 h at 25—30 °C under Ar (TLC monitoring), diluted with 15 mL of H_2O, and extracted with ether (3×6 mL). The combined ethereal extract was washed with 10% H_2SO_4 and water, dried with Na_2SO_4, and concentrated *in vacuo*. The crystalline residue (39 mg), containing, according to TLC, two less polar substances in addition to the major product, was chromatographed on a column with 1 g of SiO_2. Elution with a 6 : 4 hexane—ether mixture gave the minor products and elution with a 4 : 6 mixture of the same solvents gave 27 mg (72%) of 11,12-dihydroxydrim-8(9)-en-7-one (**2**), m.p. 94.5—95.5 °C (from hexane), $[\alpha]_D^{20}$ +63.7° (*c* 0.6). Found (%): C, 71.46; H, 9.45. $C_{15}H_{24}O_3$. Calculated (%): C, 71.42; H, 9.52. IR, ν/cm^{-1}: 1065, 3400 (br, OH); 1645 (C=C—C=O). ^{1}H NMR (200.13 MHz), δ: 0.90 (s, 3 H, C(13)H_3); 0.94 (s, 3 H, C(14)H_3); 1.17 (s, 3 H, C(15)H_3); 4.36, 4.44 (both s, each 2 H, C(11)H_2, C(12)H_2).

The authors are grateful to E. Trivellone and S. Zambardino for recording the NMR spectra and to G. Scognamiglo for spectrophotometric measurements (ICMIB, CNR, Arco Felice, Napoli, Italy).

This work was financially supported by the INTAS (Grant 96-1109).

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Received April 19, 1999;
in revised form August 6, 1999