Synthesis of 5,6-dehydro-7-oxoisodrimenin from drim-8-en-7-one

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The natural drimane sesquiterpenoid lactone 5,6-dehydro-7-oxoisodrimenin was synthesized from drim-8-en-7-one as well as from 7-oxoisodrimenin.

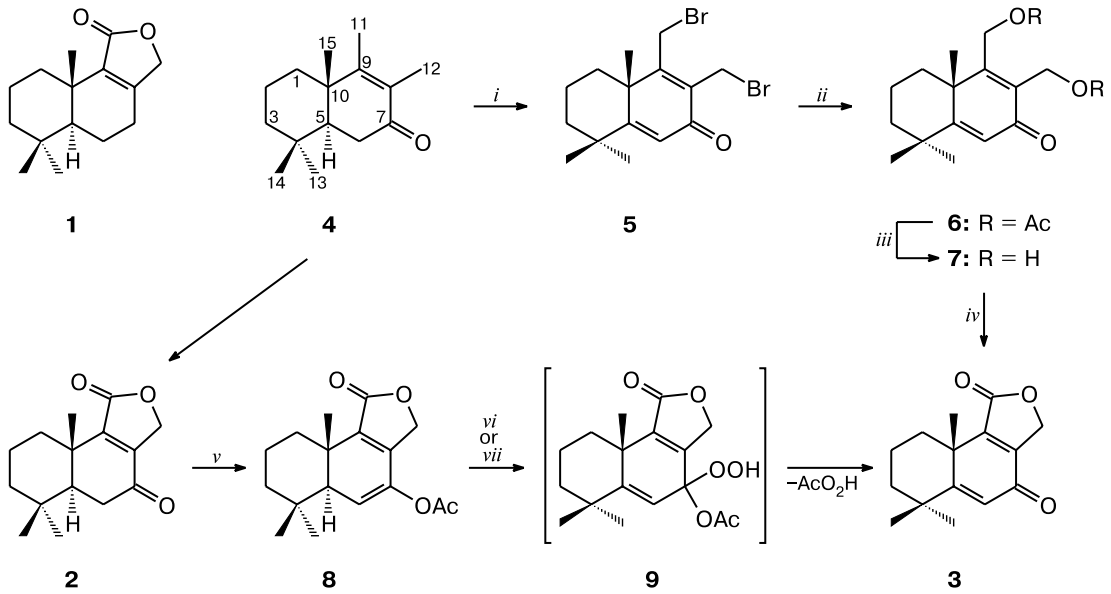
Key words: drimane sesquiterpenoids, synthesis, drim-8-en-7-one, 5,6-dehydro-7-oxoisodrimenin, photooxygenation.

Drimane-type sesquiterpenoids still attract attention of researchers due to a broad spectrum of their biological activities. This group of sesquiterpenoids includes some metabolites of American liverwort *Porella cordeana*, *viz.*, isodrimenin (**1**), 7-oxoisodrimenin (**2**), and 5,6-dehydro-7-oxoisodrimenin (**3**)[1,2] (Scheme 1). Although the latter two oxo lactones do not possess practically useful biological activities, they are of interest as starting compounds for the preparation of polyfunctional natural biologically active drimanes.

Earlier,[3] we have synthesized lactone **2** starting from readily accessible drim-8-en-7-one (**4**). In the present study, we prepared 5,6-dehydro-7-oxoisodrimenin (**3**) from the same ketone **4**.

Previously,[4] we have found that the reaction of ketone **4** with NBS under specific conditions afforded 11,12-dibromodrima-5,8-dien-7-one (**5**) in good yield (76%). The latter smoothly reacted with AcOK in DMSO to give 11,12-diacetoxydrima-5,8-dien-7-one (**6**) in high yield. Saponification of **6** with K_2CO_3 in methanol under mild conditions in an inert atmosphere produced 11,12-dihydroxydrima-5,8-dien-7-one (**7**) in satisfactory yield. It should be noted that dihydroxy ketone **7** is a labile compound and undergoes further transformations under more

Scheme 1



Reagents and conditions: *i*. NBS, CCl_4, Δ, 2 h, yield 76%; *ii*. AcOK, DMSO, 29 °C, 2 h, yield 95%; *iii*. K_2CO_3, MeOH, 29 °C, 1 h, yield 60%; *iv*. PCC, Me_2CO, 22 °C, 2 h, yield 98%; *v*. $AcOC(Me)=CH_2$, TsOH, Δ, 2 h, yield 78%; *vi*. O_2, *h*ν, Rose Bengal, 12 °C, 19 h, yield 57%; *vii*. O_2, *h*ν, H_2tpp, 12 °C, 14 h, yield 69%.

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drastic conditions (strong alkali, heating of the reaction mixture, exposure to atmospheric oxygen) to give complex mixtures of compounds. The structure of compound **7** was confirmed by spectroscopic data and elemental analysis. The assignment of the signals in the ^{13}C NMR spectra was made on the basis of DEPT experiments and by comparing with the ^{13}C NMR spectra of related compounds studied earlier.[1,3,5]

Oxidation of compound **7** with pyridinium chlorochromate (PCC) afforded oxo lactone **3** in virtually quantitative yield. Its spectroscopic characteristics are identical with those reported earlier.[1,6] However, unlike the compound described in the literature,[1] oxo lactone **3** prepared in the present study appeared to be a crystalline rather than amorphous compound. The optical rotation values of these compounds are also substantially different (by a factor of 15!), although the signs of optical rotation are identical. The melting point and specific rotation of compound **3** measured in the present study are close to the corresponding values published in the literature.[6] Hence, oxidation of dihydroxy ketone **7** proceeded regioselectively, only the hydroxy group at the C(11) atom being oxidized. The regioselectivity of the reaction results from the fact that the hydroxy group at the C(11) atom is a vinylog of the α-ketol group, which is readily oxidized.

We also synthesized oxo lactone **3** by another procedure starting from compound **2**. Enol acetate **8**, which was prepared by the TsOH-catalyzed reaction of compound **2** with isopropenyl acetate, was dehydrogenated to give oxo lactone **3** on photooxygenation in the presence of tetraphenylporphyrin (H_2tpp) or Rose Bengal as photosensitizers. It should be noted that H_2tpp is a more efficient catalyst than Rose Bengal. Apparently, this transformation is explained by the fact that singlet oxygen generated in the presence of the photosensitizer adds not at positions 1,4 of the diene system of enol acetate **8** but at the C(6) atom with the simultaneous shift of the double bond from the position C(6)—C(7) to C(5)—C(6) giving rise to hydroperoxide **9**. This intermediate is unstable and is transformed into oxo lactone **3** through elimination of a molecule of peracetic acid.

To summarize, we synthesized 5,6-dehydro-7-oxoisodrimenin (**3**) from drim-8-en-7-one (**4**) by two different procedures: 1) in four steps according to the scheme **4** → **5** → **6** → **7** → **3** in a total yield of 42.5% and 2) in six steps *via* 7-oxoisodrimenin (**2**) and its enol acetate **8** in a total yield of 22.4%.

It should be noted that oxo lactone **3** has been prepared earlier[6] by dehydrogenation of oxo lactone **2** with SeO_2. However, oxo lactone **3** thus prepared was contaminated with selenium and, apparently, organoselenium compounds, which could only be removed with difficulty by treating the reaction product with freshly precipitated silver.

Experimental

The melting points were measured on a Boetius hot-stage apparatus. The IR spectra were recorded on a Specord-74 spectrophotometer in CCl_4. The UV spectra were measured on a Specord UV-VIS spectrophotometer in MeOH. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz, respectively) in $CDCl_3$ with Me_4Si as the internal standard. The specific rotation was measured on a JASCO DIP-370 polarimeter in $CHCl_3$. Photooxygenation was carried out with the use of an OSRAM DULUX EL 15 W lamp (Germany). Column chromatography was carried out on Acros silica gel (60/200 μm). The TLC analysis was carried out on Sorbfil plates and plates with a fixed layer of SiO_2 (LS, 5/40 μm) containing 13% gypsum.

Acetoxylation of 11,12-dibromodrima-5,8-dien-7-one (5). Potassium acetate (0.261 g, 2.66 mmol) was added to a solution of dibromo ketone **5** (0.5 g, 1.33 mmol) in DMSO (8.3 mL) and the reaction mixture was stirred at 29 °C for 2 h. Then water (100 mL) was added and the reaction mixture was extracted with diethyl ether (3×30 mL). The extract was twice washed with water, dried with anhydrous Na_2SO_4, and filtered. The ether was evaporated *in vacuo*. The liquid residue (0.51 g) was chromatographed on a column with SiO_2 (5.1 g). Diacetoxy ketone **6** was eluted with a hexane—diethyl ether mixture (95 : 5 and 93 : 7) in a yield of 0.42 g (95%) as a yellowish liquid, $[\alpha]_D^{23}$ +32.9 (*c* 0.34). Found (%): C, 68.25; H, 8.04. $C_{19}H_{26}O_5$. Calculated (%): C, 68.24; H, 7.84. IR (film), ν/cm^{-1}: 1237, 1720 (OAc), 1639, 1663 (conjugated C=C), 1705 (conjugated C=O). ^1H NMR, δ: 1.26 (s, 3 H, C(13)H_3); 1.31 (s, 3 H, C(14)H_3); 1.40 (s, 3 H, C(15)H_3); 2.05 (s, 3 H, OAc); 2.09 (s, 3 H, OAc); 4.96 (s, 2 H, C(11)H_2); 4.99 and 5.02 (both d, 1 H each, C(12)H_2, J = 8.6 Hz); 6.39 (s, 1 H, C(6)H).

Saponification of 11,12-diacetoxydrima-5,8-dien-7-one (6). A 1% K_2CO_3 solution in MeOH (14 mL) was added with stirring to a solution of diacetoxy ketone **6** (0.36 g, 1.08 mmol) in MeOH (3.15 mL) at 29 °C under Ar. The reaction mixture was stirred at this temperature for 1 h, diluted with water (180 mL), and extracted with diethyl ether (3×25 mL). The extract was washed with 10% H_2SO_4 and a saturated solution of NaCl, dried with anhydrous Na_2SO_4, and filtered. The ether was distilled off *in vacuo*. According to the TLC data, the liquid residue (0.25 g) contained four compounds, with one compound predominating. The residue was chromatographed on a column with SiO_2 (5.6 g). A mixture of three compounds was eluted with a gradient hexane—diethyl ether mixture (10→30% Et_2O) in a yield of 17 mg, and this mixture was discarded. Crystalline dihydroxy ketone **7** was eluted with a hexane—30% Et_2O mixture in a yield of 162 mg (60%), m.p. 123—124.5 °C (from a hexane—diethyl ether mixture), $[\alpha]_D^{23}$ +48.3 (*c* 0.5). Found (%): C, 71.78; H, 9.03. $C_{15}H_{22}O_3$. Calculated (%): C, 71.96; H, 8.85. IR (Nujol), ν/cm^{-1}: 1050, 3310 (band) (OH), 1595, 1615 (conjugated C=C), 1650 (α,β-unsaturated ketone). ^1H NMR, δ: 1.21 and 1.29 (both s, 3 H each, C(4)(CH_3)$_2$); 1.38 (s, 3 H, C(15)H_3); 4.39 and 4.49 (both d, 1 H each, C(12)H_2, J = 12.2 Hz); 4.53 and 4.69 (both d, 1 H each, C(11)H_2, J = 12.2 Hz); 6.32 (s, 1 H, C(6)H). ^{13}C NMR, δ: 17.97 (C(2)); 24.69 (C(15)); 28.27 (C(14)); 32.29 (C(13)); 34.14 (C(1)); 37.57 (C(4)); 40.31 (C(10)); 43.64 (C(3)); 56.12 (C(12)); 58.56 (C(11)); 123.74 (C(6)); 134.73 (C(8)); 165.88 (C(9)); 173.89 (C(5)); 187.02 (C(7)).

Oxidation of 11,12-dihydroxydrima-5,8-dien-7-one (7). Pyridinium chlorochromate (108 mg, 0.5 mmol) was added to a solution of dihydroxy dienone **7** (25 mg, 0.1 mmol) in acetone (0.7 mL). The reaction mixture was stirred at 22 °C for 3 h until the reaction was completed (TLC control) and then filtered through a column with SiO_2 (1.5 g). The column was washed with diethyl ether (25 mL) and the filtrate was concentrated *in vacuo*. Crystalline oxo lactone **3** was obtained in a yield of 24 mg (97.5%), m.p. 98—100 °C (from hexane), $[\alpha]_D^{23}$ +23.3 (*c* 0.27). UV, λ_{max}/nm: 249.8 (ε 9766). IR, ν/cm^{-1}: 1664 (conjugated C=C), 1693 (conjugated C=O), 1780 (α,β-unsaturated γ-lactone). ^{1}H NMR, δ: 1.27 and 1.36 (both s, 3 H each, C(4)$(CH_3)_2$); 1.59 (s, 3 H, C(15)H_3); 4.98 and 5.05 (both d, 1 H each, C(12)H_2, J = 17.6 Hz); 6.42 (s, 1 H, C(6)H). ^{13}C NMR, δ: 17.59 (C(2)); 23.92 (C(15)); 27.70 (C(14)); 32.69 (C(13)); 34.36 (C(1)); 38.27 (C(4)); 40.90 (C(10)); 41.31 (C(3)); 67.44 (C(12)); 124.80 (C(6)); 149.56 (C(8)); 149.68 (C(9)); 170.73 (C(11)); 177.00 (C(5)); 182.46 (C(7)). Lit. data[1]: $[\alpha]_D$ +1.5 ($CHCl_3$); lit. data[6]: m.p. 100—102 °C, $[\alpha]_D$ +21 (C_6H_6), λ_{max}(EtOH) = 248 nm.

Synthesis of enol acetate 8. Toluene-*p*-sulfonic acid (2 mg) was added to a solution of oxo lactone **2** (60 mg, 0.242 mmol) in isopropenyl acetate (0.75 mL). The reaction mixture was refluxed for 2 h and then diethyl ether (30 mL) was added. The mixture was washed with a saturated solution of $NaHCO_3$ and a solution of NaCl, dried with anhydrous Na_2SO_4, and filtered. The solvent was evaporated *in vacuo*. The residue (69 mg), which was a mixture of four compounds, was chromatographed on a column with SiO_2 (2 g). The starting oxo lactone **2** and then liquid 7-acetoxy-6,7-dehydroisodrimenin (**8**) were eluted with a hexane—7.5% Et_2O mixture in yields of 7.2 mg (12%) and 46.5 mg (74.8% with account of the recovery of the starting compound), respectively. Found (%): C, 70.56; H, 7.90. $C_{17}H_{22}O_4$. Calculated (%): C, 70.32; H, 7.64. UV, λ_{max}/nm: 290 (ε 3067). IR, ν/cm^{-1}: 1190, 1740 (OAc), 1595, 1632, 1673 (conjugated C=C), 1760 (α,β-unsaturated γ-lactone). ^{1}H NMR, δ: 0.86 and 0.92 (both s, 3 H each, C(4)Me_2); 1.03 (s, 3 H, C(15)H_3); 2.15 (s, 3 H, OAc); 2.35 (d, 1 H, C(5)H, J = 3 Hz); 4.62 (s, 2 H, C(12)H_2); 5.88 (d, 1 H, C(6)H, J = 3 Hz).

Photooxygenation of 7-acetoxy-6,7-dehydroisodrimenin (8). ***A.*** The photosensitizer Rose Bengal (1.5 mg) was added to a solution of enol acetate **8** (15 mg, 0.052 mmol) in dry CCl_4 (4 mL). Then dry O_2 was bubbled with stirring through the reaction mixture at 12 °C for 19 h on irradiation of the solution with a fluorescent lamp. It was impossible to monitor the course of the reaction by TLC, because R_f of the reaction product was identical with R_f of the starting compound in different systems. The solvent was evaporated *in vacuo* and the crystalline residue (17.5 mg) was chromatographed on a column with SiO_2 (0.5 g). The column was washed with a hexane—diethyl ether mixture with an increasing ether content. Oxo lactone **3** was eluted with a hexane—20% Et_2O mixture in a yield of 7.3 mg (57%), m.p. 98—100 °C (from hexane). The spectroscopic characteristics of the resulting compound were identical with those given above.

B. Tetraphenylporphyrin (1 mg) was added to a solution of enol acetate **8** (12 mg, 0.041 mmol) in dry CCl_4 (5 mL). Then dry O_2 was bubbled with stirring through the reaction solution at 12 °C on irradiation with a fluorescent lamp for 14 h. The solvent was removed *in vacuo*. The residue, which was a mixture of three compounds, was chromatographed on a column with SiO_2 (0.5 g). Oxo lactone **3** was eluted with a hexane—20% Et_2O mixture in a yield of 7 mg (69%), m.p. 98—100 °C (from hexane). The spectroscopic characteristics of the resulting compound were identical with those given above.

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