Synthesis of isodrimenin from drim-8-en-7-one

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A naturally occurring drimanic sesquiterpenic lactone, isodrimenin, was synthesized from drim-8-en-7-one (**1**). Compound **1** was converted to the known 11,12-dihydroxydrim-8-en-7-one, which was oxidized with PCC to give 7-oxoisodrimenin. The thioketal of the latter compound was reduced with nickel boride or Raney nickel to give the target isodrimenin.

Key words: drimanic sesquiterpenoids, synthesis, isodrimenin, drim-8-en-7-one.

Recently we have transformed drim-8-en-7-one (**1**) into 11,12-acetoxydrim-8-en-7-one (**2**).[1] The product of its deacetylation, 11,12-dihydroxydrim-8-en-7-one (**3**), was then converted by T. Nacata *et al.*[2] to warburganal (**4**), the naturally occurring compound with strong antifeedant properties.

We herein report a short and effective synthesis of the naturally occurring sesquiterpenic lactone, isodrimenin, from ketodiol **3**.

Oxidation of ketodiol **3** with excess of MnO_2 or with 2 equiv. of pyridinium chlorochromate (PCC) results in the formation of a mixture of two compounds, which were separated by chromatography (see Scheme 1). According to the physicochemical and spectral data, the less polar product turned out to be a known lactone of 12-hydroxy-7-oxodrim-8-en-11-onic acid (**6**),[3,4] and the more polar substance was cyclic 11-hydroxy-11,12-epoxydrim-8-en-7-one (**7**), previously unknown. The structure of the latter was established on the basis of elemental analysis and spectroscopy data (see the Experimental section). Oxidation of ketodiol **3** with excess of PCC yielded only one product, 7-ketoisodrimenin (**6**), that is, the ketohemiacetal **7** initially generated undergoes further oxidation to ketolactone **6** under the reaction conditions. This was confirmed by the individual experiment. Thus, the oxidation of ketodiol **3** is chemoselective and regiospecific, as it involves the only hydroxyl group at the C(11) atom. It seems to be interesting to compare this process with the oxidation of drim-8-en-11,12-diol (**9**) with MnO_2 previously reported[3], which results in the formation of a mixture of isodrimenin (**5**) and confertifolin (**10**), the latter being predominant. Thus, in the case of diol **9** both its hydroxyl groups participated in the interaction, but the hydroxyl group at the C(12) atom was predominantly oxidized as the more sterically accessible. Such a difference in the behavior of compounds **3** and **9** at the oxidation can obviously be explained by the fact that in the case of ketodiol **3** only product **8**, which is the more thermodynamically stable, with the aldehyde group being conjugated with the double bond at C(8) and the keto group at C(7), is generated. It is also possible that the keto group of **3** deactivates the hydroxyl group at C(12) due to the formation of an intramolecular hydrogen bond.

It should be noted that, according to the ^1H NMR spectroscopy data, ketoacetal **7** exists as an equilibrium mixture of α- and β-epimers (**7a** and **7b**) in $CDCl_3$ solution, compound **7b** with the β-oriented hydroxyl group at C(11) being predominant. Actually, the ^1H NMR spectrum of this mixture contains two signals of the methyl group at C(10) at 1.21 and 1.34 ppm. This methyl group should be less shielded in epimer **7b**, where the hydroxyl group at C(11) is β-oriented. The ratio of intensities of the signals at 1.34 and 1.21 ppm is ~67 : 33; that is also proved by the ratio of intensities of the signals of the protons at C(11) at 6.22 and 6.15 ppm.

7-Ketoisodrimenin (**6**) reacts smoothly with $(CH_2SH)_2$ in the presence of $BF_3 \cdot Et_2O$ or $SnCl_2$ yielding thioketal **11**. The latter procedure[5] is, however, more effective and convenient. Reduction of thioketal **11** with Raney nickel T-1[6] or, which is more effective, with nickel boride, prepared by the method[7] from $NiCl_2 \cdot 6H_2O$ and $NaBH_4$, resulted in the formation of isodrimenin (**5**). Its total yield was 30.6% from drim-8-en-7-one (**1**) (6 steps) in the optimum variant.

Thus, we have performed short and effective synthesis of the naturally occurring drimanic

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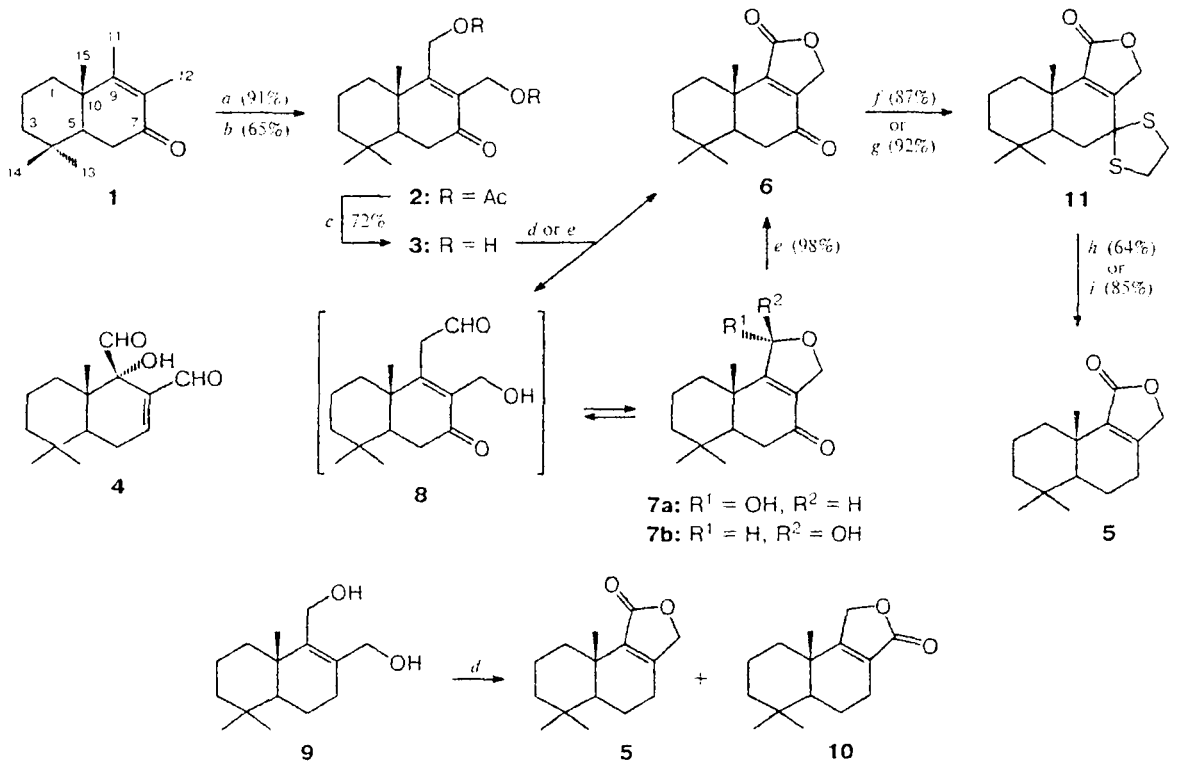
Scheme 1



Reagents and conditions: *a*) NBS, CCl_4, Δ, 2 h; *b*) AcOK, DMSO, 20 °C, 1 h; *c*) K_2CO_3, MeOH, 25 °C, 3 h; *d*) MnO_2, CH_2Cl_2, 20 °C, 48 h; *e*) PCC, CH_2Cl_2, 20 °C, 1 h; *f*) $(CH_2SH)_2$, AcOH, $BF_3 \cdot Et_2O$, 20 °C, 18 h; *g*) $(CH_2SH)_2$, $SnCl_2 \cdot 2H_2O$, THF, Δ, 0.5 h; *h*) Raney Ni, dioxane, Δ, 5 h; *i*) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, DMF, 20 °C, 20 min.

sesquiterpenic lactone isodrimenin (**5**) from available drim-8-en-7-one (**1**).

Experimental

Melting points were taken on a Boetius hot-stage. IR spectra were recorded on a Specord 74 instrument in CCl_4. UV spectra were recorded on a Specord M-40 spectrophotometer. ^1H NMR spectra were registered on Varian 300 and Bruker AM-400 spectrometers in $CDCl_3$ with Me_4Si as the internal standard. The specific optical rotations were measured on a Jasco DIP polarimeter in $CHCl_3$. Column chromatography was performed on silica gel L (40/100 and 100/160 μm) and Acros (60/200 μm). TLC was carried out on plates with a fixed SiO_2 LS (5/40 μm) layer containing 13% of gypsum or on Silufol (Czech Republic) plates. The solutions of compounds in organic solvents were dried over anhydrous Na_2SO_4.

Oxidation of 11,12-dihydroxydrim-8-en-7-one (3). *A.* Pyridinium chlorochromate[8] (0.25 g, 1.2 mmol) was added to a solution of 0.15 g (0.6 mmol) of compound **3** in CH_2Cl_2 (3.5 mL), and the mixture was kept at 20 °C until the reaction was complete (1 h, TLC control). The reaction mixture was filtered through a column with a short SiO_2 layer, and the column was washed with diethyl ether. The filtrate was evaporated *in vacuo*. The residue (0.142 g) was chromatographed on a column with 4.5 g of SiO_2. Elution with a hexane–diethyl ether (9 : 1) mixture gave 70 mg (47%) of lactone of 12-hydroxy-7-oxodrim-8-en-11-onic acid, 7-ketoisodrimenin (**6**), m.p. 117–118 °C (from hexane), $[\alpha]_D$ +36.9° (*c* 1.6; C_6H_6). UV, λ_{max}^{EtOH} 247 nm (ε 10550). IR, ν/cm^{-1}: 1693 (α,β-unsaturated cyclohexanone) and 1777 (α,β-unsaturated γ-lactone). ^1H NMR (300 MHz, δ): 0.94 and 0.97 (both s, 2×3 H, C(4)$(CH_3)_2$); 1.30 (s, 3 H, C(10)CH_3); 1.90 (dd, 1 H, C(5)H, J = 12 and 3.4 Hz); 2.51 (dd, 1 H, C(6)H_{ax}, J = 17.6 and 13.9 Hz); 2.65 (dd, 1 H, C(6)H_{eq}, J = 17.6 and 3.4 Hz); and 4.84 (s, 2 H, C(12)H_2). ^{13}C NMR (50 MHz, δ): 17.94 (C(2)), 18.10 (C(15)), 21.04 (C(14)), 32.83 (C(13)), 33.14 (C(4)), 33.25 (C(1)), 36.14 (C(6)), 35.72 (C(10)), 41.11 (C(3)), 52.07 (C(5)), 67.30 (C(12)), 149.10 (C(8)), 152.55 (C(9)), 170.89 (C(11)), and 196.36 C(7)). Lit.[4]: m.p. 112–113 °C, $[\alpha]_D$ +52° (C_6H_6). Elution with a hexane–diethyl ether (8 : 2) mixture gave 59 mg (40%) of 11-hydroxy-11,12-epoxydrim-8-en-7-one (**7**), m.p. 132–133 °C (from MeCN). Found (%): C, 72.13; H, 9.00. $C_{15}H_{22}O_3$. Calculated (%): C, 71.97; H, 8.86. UV, λ_{max}^{EtOH} 241 nm (ε 8750). IR (Vaseline), ν/cm^{-1}: 1035, 1059 (epoxide), 1653 (α,β-unsaturated ketone), and 3319 (band) (OH). ^1H NMR (300 MHz, δ): 0.90 and 0.91 (both s, 3 H), 0.95 and 0.96 (both s, 3 H) (C(4)$(CH_3)_2$); 1.21 and 1.34 (both s, 3 H, C(10)CH_3); 2.49 (m, 2 H, C(6)H_2); 4.60 (d, J = 13.2 Hz) and 4.61 (d, J = 13.1 Hz) (1 H), 4.84 (t, J =

13.1 Hz) and 4.85 (t, J = 13.0 Hz) (1 H) (C(12)H_2); 6.15 and 6.22 (both d, 1 H, C(11)H). The ratio of the integral intensities of the signals at 6.15 and 6.22 ppm is ~33 : 67; that is in agreement with the ratio of the intensities of the signals at 1.21 and 1.34 ppm.

B. Manganese dioxide (1.7 g, 20 mmol) was added to a solution of 0.2 g (0.79 mmol) of compound **3** in CH_2Cl_2 (10 mL), and the mixture was stirred at 20 °C until the reaction was complete (45 h, TLC control). The precipitate of MnO_2 was filtered and washed with CH_2Cl_2. The filtrate was evaporated *in vacuo*. The residue (154 mg) was chromatographed on a column with 5 g of SiO_2 to give 55 mg (28%) of 7-ketoisodrimenin (**6**) and 70 mg (35%) of hemiacetal **7**.

C. Pyridinium chlorochromate (237 mg, 1.1 mmol) was added to a solution of 55 mg (0.22 mmol) of compound **3** in CH_2Cl_2 (1.5 mL), and the mixture was stirred at 28 °C until the reaction was complete (1.5 h, TLC control). The reaction mixture was treated as described in *A* to give 50 mg (92%) of 7-ketoisodrimenin (**6**).

Oxidation of hemiacetal 7. Pyridinium chlorochromate (17 mg, 0.08 mmol) was added to a solution of 10 mg (0.04 mmol) of compound **7** in CH_2Cl_2 (0.25 mL). The mixture was stirred at 28 °C for 1 h and treated as described above to give 9.7 mg (98%) of 7-ketoisodrimenin (**6**), m.p. 117–118 °C (from hexane).

Thioketalization of 7-ketoisodrimenin (6). *A.* Ethane-1,2-dithiol (0.085 mL, 1 mmol) and 0.05 mL of $BF_3 \cdot Et_2O$ were added to a solution of 120 mg (0.48 mmol) of compound **6** in 1 mL of glacial AcOH. The mixture was kept at 20 °C until the reaction was complete (18 h, TLC control), diluted with 30 mL of diethyl ether, washed with 10% NaOH (3×10 mL) and water (3×10 mL), dried, filtered, and evaporated. The residue (200 mg, mixture of three compounds) was chromatographed on a column with 5 g of SiO_2 in the hexane–diethyl ether gradient. A mixture of hexane–diethyl ether (99 : 1) eluted the mixture of two compounds (12 mg), which were not investigated. The mixture of the same solvents (97.5 : 2.5) eluted 137 mg (87%) of 7,7-ethylenedithio-12-hydroxydrim-8-en-11-oic acid lactone **11**, m.p. 82–83 °C (from the hexane–diethyl ether mixture). Found (%): C, 63.35; H, 7.54; S, 19.47. $C_{17}H_{24}O_2S_2$. Calculated (%): C, 62.92; H, 7.46; S, 19.76. IR, ν/cm^{-1}: 1455 (thioketal) and 1760 (α,β-unsaturated γ-lactone). ^1H NMR (300 MHz, δ): 0.90 (s, 3 H), 0.99 (s, 3 H) (C(4)$(CH_3)_2$); 1.18 (s, 3 H, C(10)CH_3); 3.42 (m, 4 H, SCH_2CH_2S); 4.92 (s, 1 H), and 4.94 (s, 1 H) (C(12)H_2).

B. Ethane-1,2-dithiol (0.085 mL, 1 mmol) and 6 mg of $SnCl_2 \cdot 2H_2O$ were added to a solution of 150 mg (0.6 mmol) of 7-ketoisodrimenin (**6**) in 5 mL of THF, and the mixture was refluxed until the reaction was complete (0.5 h, TLC control). The mixture was diluted with 15 mL of water and extracted with diethyl ether (3×20 mL). The extract was washed with 10% NaOH (10 mL) and water to pH 7 (3×10 mL), dried, filtered, and evaporated *in vacuo*. The residue was chromatographed on a column with 7.2 g of SiO_2. Elution with hexane–diethyl ether (9 : 1) gave 180 mg (92%) of thioketal **11** identical to that obtained in *A*.

Reduction of 7-ketoisodrimenin thioketal (11). *A.* Raney nickel obtained from 1.3 g of Ni–Al (1 : 1) alloy by the method[7] was added to a solution of 80 mg of thioketal **11** in 4 mL of dioxane, and the mixture was refluxed for 5 h. The catalyst was filtered off, and the solvent was evaporated *in vacuo* to give 37 mg (64%) of isodrimenin (**5**), m.p. 131–132 °C (from hexane). $[\alpha]_D^{20}$ +89.3° (*c* 0.5, $CHCl_3$). IR, ν/cm^{-1}: 1765 (α,β-unsaturated γ-lactone) and 1673 (conjugated double bond). ^1H NMR (400 MHz, δ): 0.92 (s, 3 H) and 0.96 (s, 3 H) (C(4)$(CH_3)_2$); 1.17 (s, 3 H, C(10)CH_3); 4.56 and 4.61 (the centers of gravity of the two doublets of the AB-system, 2 H, C(12)H_2, J = 16 Hz). ^{13}C NMR (100 MHz, δ): 18.54 (C(2) or C(7)), 18.71 (C(7) or C(2)), 20.48 (C(15)), 21.79 (C(14)), 25.72 (C(6)), 33.35 (C(4)), 33.84 (C(13)), 34.86 (C(1)), 35.31 (C(10)), 42.22 (C(3)), 52.83 (C(5)), 70.99 (C(12)), 136.11 (C(8)), 159.45 (C(9)), and 172.85 (C(11)). Lit.[4]: m.p. 131–132 °C, $[\alpha]_D$ +87° ($CHCl_3$).

B. $NiCl_2 \cdot 6H_2O$ (2.094 g, 8.8 mmol) and then in small portions 1.714 g (17.6 mmol) of 39% $NaBH_4$ were added with stirring to a solution of 180 mg (0.55 mmol) of thioketal **11** in DMF (6.6 mL) at 15 °C, and the mixture was stirred at the same temperature until the reaction was complete (20 min, TLC control). Thioketal **11** and isodrimenin (**6**) are of the same polarity and differ only in the color of the spots on the TLC plates upon visualization by iodine vapor.[7] The mixture was diluted with 15 mL of water and extracted with diethyl ether (3×20 mL). The extract was washed with water, dried, filtered, and evaporated *in vacuo*. The residue was crystallized from hexane to give 111 mg (85%) of isodrimenin (**5**), m.p. 131–132 °C, identical to the product prepared by the method *A*.

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