SYNTHESIS OF 8α-ACETOXYDRIMAN-11-OIC ACID

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A five-stage synthesis of 8α-acetoxydriman-11-oic acid from the readily available bicyclohomofarnesane-8α,12-diol has been developed.

Thanks to the presence of functional groups at C-8 and C-11, 8α-acetoxydriman-11-oic acid (VII) is a valuable intermediate for the synthesis of a number of drimane sesquiterpenoids possessing various biological activities.

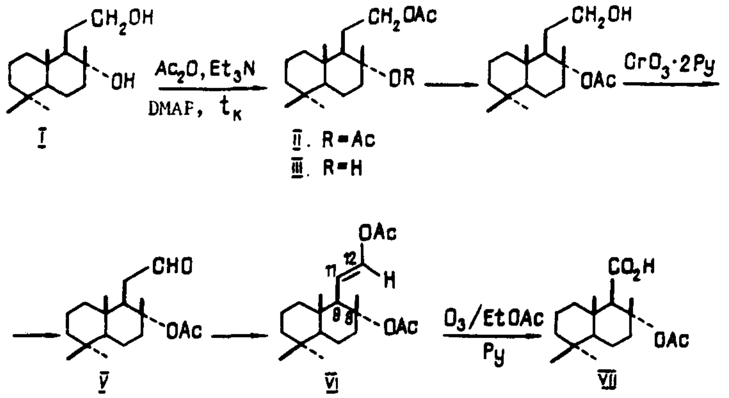
The aim of the work reported in the present communication was to develop a method for the synthesis of the acetoxy acid (VII) from bicyclohomofarnesane-8α,12-diol (I), an industrial product of the transformation of the labdane diterpenoid sclareol [1].

The acetylation of the diol (I) by the method of Steglich and Hofle [2] led to the diacetate (II) with a yield of 80%. The saponification of (II) with sodium bicarbonate in methanol at room temperature gave a mixture of bicyclohomofarnesane-8α,12-diol (I) and its 8-monoacetate (IV) (yield 58%) [3]. Attempts to improve the yield of the latter compound by varying the saponification conditions were unsuccessful.

On oxidation by the method of Collins et al. [4], the hydroxy acetate (IV) gave a 63% yield of the acetoxy aldehyde (V) [3, 5]. The interaction of the latter [6] with acetic anhydride in triethylamine in the presence of 4-dimethylaminopyridine (DMAP) formed 8α,12-diacetoxy-13,14,15-trisnorlabd-11-ene (57% yield) PMR spectroscopy showed that the product isolated was the trans-isomer of the enol acetate (VI). However, since it could be purified by crystallization only with difficulty, the enol-acetylation product was apparently a mixture of the cis- and trans-isomers with a substantial predominance of the latter.

The ozonization of the enol acetate (VI) in ethyl acetate in the presence of pyridine took place smoothly and led with 88% yield to the acetoxy acid (VII).

Thus, as a result of the investigation performed, the synthesis of 8α-acetoxydriman-11-oic acid (VII) has been performed with an overall yield of 16%, calculated on the initial bicyclohomofarnesane-8α,12-diol (I).



EXPERIMENTAL

Melting points were determined on a Boëtius instrument. Specific rotations were measured in $CHCl_3$ on a SM polarimeter. IR spectra were taken in CCl_4 on a Specord-71-IR spectrophotometer. PMR spectra were recorded in CCl_4 on a Tesla BS-467 instrument (60 MHz)

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with TMS as internal standard (the signals are given on the δ scale). Silica gel of type L 100/160 μm (Czechoslovakia) was used for column chromatography.

Preparation of the Diacetate (II). The diol (I) (1.95 g, 7.3 mmole) was dissolved in a mixture of 2.7 ml (29.12 mmole) of acetic anhydride, 1.4 ml of triethylamine, and 35 mg (0.29 mmole) of 4-dimethylaminopyridine (DMAP). The reaction mixture was kept at room temperature for 40 h. Then another 2.7 ml of acetic anhydride and 35 mg of DMAP were added to it and it was kept at the same temperature until the reaction was complete (160 h, monitoring by TLC).

The reaction mixture was diluted with 30 ml of 10% H_2SO_4 and 20 ml of H_2O and was extracted with diethyl ether. The ethereal extract was washed with 20 ml of saturated $NaHCO_3$ solution and with water and was then dried over anhydrous Na_2SO_4 and filtered, and the ether was distilled off in vacuum. The residue (2.4 g) was chromatographed on a column containing 80 g of silica gel.

Mixture of petroleum ether and ethyl acetate eluted a series of fractions of increasing polarity. The least polar of them (1.5 g), eluted by petroleum ether—ethyl acetate (9:1), was the diacetate (II), mp 57-59°C (from petroleum ether), $[\alpha]_D^{20}$ −16.2 (c 3.2). IR spectrum (cm^{-1}): 1360, 1375, $[C(CH_3)_2]$; 1240, 1720 (OAc). PMR spectrum (ppm): 0.77 (3H, s), 0.83 (3H, s), 0.87 (3 H, s), 1.42 (3 H, s, CH_3-8 (methyl groups at quaternary carbon atoms): 1.9 (3 H, s), 1.95 (3 H, s) (two OAc groups); 3.96 (2 H, m, CH_2-12). Found %: C 71.12; H 10.11. $C_{20}H_{34}O_4$. Calculated, %: C 70.96; H 10.12.

Petroleum ether—ethyl acetate (85:15) eluted from the column a mixture of the diacetate (II) with two more polar compounds (833 mg), and a (3:1) mixture of the same solvents eluted 98 mg (4.8%) of the monoacetate (III). IR spectrum (cm^{-1}): 1365, 1375 $[C(CH_3)_2]$, 1165, 3530, 3620 (OH), 1240, 1740 (OAc) [7].

Saponification of the Diacetate (II). With stirring, a solution of 320 mg (0.95 mmole) of the diacetate (II) in 5 ml of methanol was added to a solution containing 95 mg of sodium bicarbonate in 1.5 ml of water and 5 ml of methanol. The reaction mixture was stirred at at room temperature for 50 h (monitoring by TLC) and was then diluted with water and extracted with diethyl ether. The ethereal extract was washed with water, dried with anhydrous Na_2SO_4 and filtered, and the ether was distilled off. This gave 272 mg of reaction product, which was chromatographed on a column containing 6 g of silica gel. Petroleum ether—ethyl acetate (45:1) eluted 68 mg of the diacetate (II) from the column. The same mixture of solvents eluted 162 mg (58%) of the monoacetate (IV), mp 84.5-85.5°C (from petroleum ether). The chromatographic and spectral characteristics of the product were identical with those of a sample that we had obtained previously by a different method [8].

Oxidation of the Monoacetate (IV). The monoacetate (IV) (330 mg, 1.11 mmole) was oxidized with 866 mg (3.33 mmole) of the complex $CrO_3 \cdot 2Py$ in 10 ml of methylene chloride at room temperature for 12 h. After the usual working up, 306 mg of a product was obtained which was chromatographed on a column containing 2 g of silica gel. Petroleum ether eluted 192 mg (63%) of the acetoxy aldehyde (V), mp 75.5-77.5°C (from aqueous methanol). IR spectrum (cm^{-1}): 1360, 1380 $[C(CH_3)_2]$; 1237, 1730 (OAc); 1725, 2708 (CHO). The substance gave no depression of the melting point with a sample of the aldehyde (V) [3]. Their IR spectra coincided.

Preparation of the Enol Acetate (VI). To 192 mg (0.65 mmole) of the acetoxy aldehyde (V) was added 3 ml of acetic anhydride, 0.3 ml (2.3 mmole) of triethylamine, and 10 mg (0.08 mmole) of DMAP. The reaction mixture was kept at room temperature for 14 h, and, after the addition of another 0.1 ml of acetic anhydride, 0.1 ml of triethylamine, and 5 ml of DMAP, it was heated at 50°C for 138 h (monitoring by TLC). The reaction mixture was diluted with water (30 ml) and was extracted with diethyl ether. The ethereal extract was washed with water, dried, and filtered, and the ether was distilled off. The residue (140 mg) was chromatographed on a column containing 6 g of silica gel. Petroleum ether—ethyl acetate (49:1) eluted 120 mg of the enol acetate (VI), mp 83-84°C (from petroleum ether), $[\alpha]_D^{20}$ -48.2° (c 2.9).

IR spectrum (cm^{-1}): 840, 1670, 3085 (trisubstituted double bond), 1375, 1380 $[C(CH_3)_2]$, 1225, 1250, 1720, 1760 (two OAc). PMR spectrum (ppm): 0.77 (3H, s), 0.85 (6H, s) (methyl groups at C-10 and C-4), 1.2 (3H, s, CH_3 at C-8), 1.80 (3H, s), 2.02 (3H, s) (two AcOH groups) 3.17 (1H, d, J = 12 Hz, H-9), 5.25 (1H, t, J = 12 Hz, H-11), 6.85 (1H, d, J = 12 Hz, H-12). Found, %: C 71.70; H 9.85. $C_{20}H_{32}O_4$. Calculated, %: C 71.39; H 9.58.

Ozonation of the Enol Acetate (VI). A mixture of ozone and oxygen was passed at −65 to −70°C through a solution of 170 mg of the enol acetate in 17 ml of ethyl acetate and 0.85 ml of pyridine until ozone appeared at the outlet of the reaction flask (25 min). The excess of ozone was eliminated by passing dry gaseous nitrogen through the solution, which was then poured into 30 ml of a 1% solution of NaOH and extracted with diethyl ether. The ethereal extract was washed with water, dried with anhydrous Na_2SO_4, and filtered, and the ether was distilled off. This gave 30 mg of a neutral fraction consisting of the enol acetate (VI).

The aqueous solution was acidified with 10% H_2SO_4 solution and extracted with diethyl ether. The ethyl extract was washed with water, dried, and filtered, and the ether was distilled off. This gave 125 mg of 8α-acetoxydriman-11-oic acid (VII), mp 144-145°C (from petroleum ether) $[\alpha]_D^{20}$ -39.74° (c 2.72). IR spectrum (cm^{-1}): 1240, 1720 (OAc), 1700 ($>C{=}O$), 2400-3550 ($-C-OH$), 1370, 1385 [$C(CH_3)_2$]. PMR spectrum (ppm): 0.75 (3H, s, CH_3-10), 0.82 (3H, s, CH_3-10), 0.82 (3H, s, CH_3-4), 1.08 (3H, s, CH_3-4), 1.6 (3H, s, CH_3-8), 1.82 (3H, s, $CH_3-C{=}O$), 10.35 (1H, s, CO_2H). Found %: C 68.82; H 9.92. $C_{17}H_{28}O_4$. Calculated %: C 68.88; H 9.52.

LITERATURE CITED

1. P. F. Vlad and M. N. Koltsa, The Synthesis and Use of Odoriferous Substances from Labdane Diterpenoids [in Russian], Shtiintsa, Kishinev (1988), p. 130.
2. W. Steglich and G. Hofle, Angew. Chem. Int. Ed. Engl., 8, 981 (1969).
3. E. J. Corey, H. J. Hess, and S. Proskow, J. Am. Chem. Soc., 85, No. 24, 3979 (1963).
4. J. C. Collins, W. W. Hess, and F. J. Frank, Tetrahedron Lett., 3363 (1968).
5. H. L. Stoll and M. Hinder, Helv. Chim. Acta, 33, No. 5, 1251 (1950).
6. T. J. Cousineau, S. L. Cook, and J. A. Secrist, Synth. Commun., 9, No. 3, 157 (1979).
7. P. F. Vlad, G. A. Dragalina, and M. N. Koltsa, Zh. Obshch. Khim., 47, No. 4, 943 (1977).
8. A. N. Aryku, M. N. Koltsa, and P. F. Vlad, Khim. Prir. Soedin., 209 (1991).

INVESTIGATION OF THE PRODUCTS OF THE OZONOLYSIS OF SCLAREOL AND THE PATHWAYS FOR THEIR FORMATION

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It has been established that the main products of the ozonolysis of sclareol (I) under various conditions are "sclareol oxide" (III), 8α-hydroxy-14,15-bisnorlabdan-13-ome (IV), and the new compound (13R,14R)-14-hydroperoxy-13,14-epoxy-14-norlabdan-8α-ol (X), and structure of which has been shown on the basis of its transformations. The acid fraction of the ozonation products, the yield of which was low (<8%) included two compounds: sclareolic acid (85%) and 18α-hydroxy-14,15,-16-trisnorlabdan-13-oic acid (3%). The mechanism for the formation of the above-mentioned compounds is discussed.

Continuing a series of studies on the products of the ozonolysis of readily available labdane diterpenoids, in the present communication, we give the results of an investigation of the ozonization of the labdanoid sclareol (I), which is of practical importance.

It must be mentioned that little attention has been devoted to the ozonization of sclareol. Janot [1] ozonized sclareol in carbon tetrachloride and decomposed the ozonide by heating with water, but the reaction products remained unidentified. When the reaction was performed in methanol and the reaction product was treated with ammonium chloride, Odinokov et al. [2] obtained an oxide compound of dimeric structure (II) with a yield of 80%.

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