SYNTHESIS OF BICYCLOHOMOFARNESANE COMPOUNDS BY THE OZONIZATION OF "SCLAREOL OXIDE"

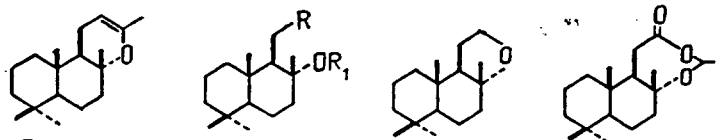
A. N. Aryku, M. N. Koltsa, and O. V. Vlad

UDC 547.596/599

Ozonolytic pathways for the selective transformation of "sclareol oxide" (I) with good yield into the bicyclohomofarnesane derivatives (II), (III), (V), and (VII) have been developed.

"Sclareol oxide" (I) is one of the most important breakdown products of the labdane diterpenoid sclareol and serves as the starting material for the synthesis of compounds of the bicyclohomofarnesane series that are valuable in practice [1]. Such compounds have been obtained in the oxidation of "sclareol oxide" (I) by compounds of manganese or chromium or by ozone [1, 2]. Ozone is used most frequently. When tbheoxide (I) was ozonized in hexane with subsequent decomposition of the ozonide by heating with water, Ruzicka et al. [2] isolated 8α-acetoxybicyclohomofarnesan-12-oic acid (II) in 24% yield. The performance of the reaction in the same solvent followed by the reduction of the ozonide with lithium tetrahydroaluminate led, according to [3], to bicyclohomofarnesane-8α,12-diol (III) (57-75%) and a small amount of ambroxide (IV) (14-1%) or, according to [4, 5], to only the diol (III) in 67% and 78% yield, respectively. When the oxide (I) was ozonized in ethyl acetate and the ozonide was treated with Raney nickel, the main reaction product was 8α-acetoxybicyclohomofarnesal (V) (~50%), and a minor product was the acetoxy acid (II) (~3%) [6]. The results proved to be better if the ozonide was decomposed by heating with water: the yields of compounds (V) and (VI) were, respectively, 60-65 and ~3%. Among the minor products in this case the lactone acetal (VI) was identified [7]. In the present communication we give the results of a more detailed investigation of the ozonization of "sclareol oxide" (I) that we undertook with the aim of finding conditions for the planned synthesis of a number of substances of the bicyclohomofarnesane series.

We have established that the methodologically most convenient route to the acetoxy aldehyde (V) is the ozonization of the oxide (I) at −25 to −30°C in methylene chloride or ethyl acetate in the presence of a catalytic amount of pyridine (see experiments 1-4 in Table 1). The yield of acetoxy aldehyde amounted to ~80%. In addition, a small amount (13-19%) of the acetoxy acid (II) was formed. Compound (V) was identified by comparing its IR spectrum and constants with those given in [7], and the acetoxy acid (II) by a direct comparison with an authentic sample. Approximately the same results were obtained on the ozonization of the oxide (I) in hexane and the decomposition of the ozonide by heating with water (experiments 5 and 6); however, this method requires additional cleavage of the ozonide and is not without danger, particularly when the reaction is performed with a large amount of substance. As is known [6], the acetoxy aldehyde (V) is extremely unstable and is readily oxidized by air, and it is not excluded that the acetoxy acid (II) is formed during the working up of the reaction mixtures. It must be mentioned that the yields of compounds (II) and (V) did not change in the temperature range of −70 to −25°C.



I

II. R=CO_2H; R_1=Ac
III. R=CH_2OH; R_1=H
V. R=CHO; R_1=Ac
VII. R=CH_2OH; R=Ac

IV

VI

Institute of Chemistry, Academy of Sciences of the Moldavian SSR, Kishinev. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 209-214, March-April, 1991. Original article submitted June 29, 1990.

0009-3130/91/2702-0179$12.50

TABLE 1. Products of the Ozonolytic Transformation of "Sclareol Oxide" (I)*

Experiment No.	Solvent	Temperature, °C	Method of decomposing the ozonide	Yield, %			
				V	II	III	VII
1	CH_2Cl_2	−65 ÷ −70	Pyridine	82	17	—	—
2	CH_2Cl_2	−25 ÷ −30	Pyridine	80	19	—	—
3	$CH_3CO_2C_2H_5$	−65 ÷ −70	Pyridine	79	16	—	—
4	$CH_3CO_2C_2H_5$	−25 ÷ −30	Pyridine	77	13	—	—
5	Hexane	−65 ÷ −70	Water	82	10	—	—
6	Hexane	−25 ÷ −30	Water	84	12	—	—
7	Hexane	−65 ÷ −70	H_2O_2	40	57	—	—
8	Cyclohexane	18-20	SiO_2 (2 parts by weight) + 1 mole of CH_3CO_2H	64	26	—	—
9	Cyclohexane	18—20	SiO_2 (4 parts by weight) + 1 mole of CH_3CO_2H	23	62	—	—
10	Cyclohexane	18—20	SiO_2 (10 parts by weight) + 1 mole of CH_3CO_2H	11	74	—	—
11	$CH_3CO_2C_2H_5$	−25 ÷ −30	CrO_3/H_2SO_4	—	65	—	—
12	Hexane	−65 ÷ −70	$LiBH_4$** (in ether)	—	—	76	—
13	Hexane	−65 ÷ −70	$LiBH_4$** and saponification	—	—	61	—
14	Isopropanol	−65 ÷ −70	$LiBH_4$** and saponification	—	—	64	—
15	Methanol	−65 ÷ −70	$LiBH_4$**	—	10	—	62
16	Methanol	−65 ÷ −70	KBH_4 and CH_3OH	—	13	—	53

*In all the experiments 100 mg of "sclareol oxide" (I) was dissolved in 10 ml of solvent.
**Obtained in situ from KBH_4 and LiCl in isopropanol.

If the ozonide obtained in hexane was decomposed by heating with hydrogen peroxide (experiment 7) the selectivity of the reaction fell and the reaction product consisted of a mixture of compounds (V) and (II) in a ratio of 2:3. The same thing took place when the oxide (I) was ozonized in cyclohexane in the presence of 1 molar equivalent of acetic acid and a relatively small amount of silica gel, followed by the hydrogenation of the reaction product over Lindlar catalyst (ratio of substances (V) and (II) ~3:1, experiment 8). With an increase in the maount of absorbent, the yield of the acetoxy acid (II) rose and that of the acetoxy aldehyde (V) fell (experiment 9), and at a weight ratio of oxide (I) to silica gel of 1:10 (experiment 10), the main reacrion product was the acetoxy acid (II) (yield 74%), i.e., the reaction again became structurally selective. The acetoxy acid (II) also predominated (yield 65%) on the oxidative cleavage of the ozonide by an excess of the Jones reagent (experiment 11). In this case, the neutral fraction did not contain any of the acetoxy aldehyde (V).

When the oxide (I) was ozonized in hexane and the ozonide was reduced with lithium tetrahydroaluminate (experiment 12), the diol (III) was obtained with 76% yield, which agrees with information in the literature [4, 5]. If lithium tetrahydroborate, obtained in situ from potassium tetrahydroborate and lithium chloride in isopropanol [8], was used as the reducing agent and the product was then saponified with alkali, the yield of diol (III) fell to 15% and, in addition, a small amount of an acid fraction was formed which we have not investigated (experiment 13). When lithium tetrahydroborate was used as the reducing agent, it was more convenient to perform the ozonization in the same solvent, since in this case there was no necessity for eliminating the solvent from the ozonide solution although, in view of the polar nature of the solvent, peroxide products and not an ozonide should then have been formed (experiment 14).

The ozonization of oxide (I) in methanol and the reduction of the peroxides with lithium tetrahydroborate (experiment 15) or potassium tetrahydroborate (experiment 16) without saponification led to the 8-monoacetate of bicyclohomofarnesane-8α,12-diol (VII) and a small amount of the acetoxy acid (II). The diol (VII) has been described in the literature [4, 6] as a liquid substance. The product that we obtained was crystalline (mp 84.5-85.5°C). Its structure

was confirmed by its IR and PMR spectra, and also by elementary analysis. As was to be expected, its IR spectrum contained maxima charcteristic for acetate and hydroxy groups, and it sPMR spectra the singlet signals of three methyl groups at quaternary carbon atoms, one at a tertiary carbinol atom, of the methyl of an acetate group, and a triplet two-proton signal of the $-CH_2-OH$ grouping.

Thus, the facts given above show that by varying the conditions of performing the ozonolysis of the oxide (I) it is possible to obtain selectively as the main reaction product one of compounds (II), (III), (V), and (VII).

EXPERIMENTAL

For the general part, see [9].

Preparation of 8α-Acetoxybicyclohomofarnesan-12-al (V). a) A current of ozonized oxygen was passed through a solution of 100 mg of "sclareol oxide" (I) in 10 ml of dry methylene chloride and 0.1 ml of dry pyridine at the appropriate temperature until the ozone broke through. The excess of ozone was driven out with nitrogen, and the reaction mixture was left to assume room temperature, after which 10 ml of a 10% solution of sulfuric acid was added to it and it was extracted with ether (3 × 20 ml). The extract was washed with 2% caustic potash solution (2 × 15 ml) and twice with water, and it was dried with anhydrous sodium sulfate and filtered, and the solvent was evaporated off. This gave 92 mg (~82%) of a neutral compound with traces of a more polar product (TLC results) which was chromatographed on a column containing 3 g of silica gel L 40/100 μm. A mixture of diethyl ether and petroleum ether (1:9) eluted the pure 8α-acetoxybicyclohomofarnesan-12-al (V), with mp 75.5-77.5°C (from aqueous methanol). IR spectrum (cm^{-1}): 1360, 1380 (gem-dimethyl group); 1237, 1730 (OAc); 1725, 2708 (CHO). It was identical with the spectrum given in [7]. According to the literature [7]; mp 78.5-79°C.

The alkaline extract was acidified with sulfuric acid and was extracted three times with ether, the extract was washed with water to neutrality, dried with anhydrous sodium sulfate, and filtered, and the solvent was evaporated off. This gave 20 mg (17%) of an acid fraction, which was recrystallized from a mixture of diethyl ether and petroleum ether (1:3); mp 154-155°C. IR spectrum (cm^{-1}): 1362, 1387 (gem-dimethyl group); 1240, 1724 (OAc); 1705, 3100-3400 (band) (COOH). The substance was identified by direct comparison with an authentic sample. According to the literature [2] mp 157-158°C.

b) "Sclareol oxide" (100 mg) was ozonized in 10 ml of ethyl acetate and 0.1 ml of dry pyridine at the necessary temperature until saturation, and the product was worked up as described in paragraph a). The results are given in Table 1.

c) A current of ozonized oxygen was passed through a solution of 100 mg of the oxide (I) in 10 ml of hexane at the given temperture until the ozone broke through. The excess of ozone was displaced with nitrogen and the solution was allowed to warm up to room temperature, after which 20 ml of water was added and the mixture was heated to 70°C and was stirred at this temperature for 2 h. The hexane layer was washed with a 2% solution of KOH (2 × 10 ml) and with water (2 × 20 ml) and was dried with anhydrous Na_2SO_4 and filtered, and the hexane was evaporated off to give the neutral fraction (for the results, see Table 1).

The alkaline extract was acidified and worked up as described in paragraph a). The acetoxy acid (II) was isolated (Table 1).

Preparation of a Mixture of the Acetoxy Acid (II) and the Acetoxy Aldehyde (V). a) At −65 to −70°C, a current of ozonized oxygen was passed through a solution of 100 mg of the oxide (I) in 10 ml of hexane until the ozone broke through, and the solution was purged with nitrogen. The hexane was distilled off under reduced pressure in a current of argon at room temperature, the residue was treated with 20 ml of 10% hydrogen peroxide, and the mixture was kept at 70°C for 5 h. Then 20 ml of water was added to it and it was extracted with ether (3 × 20 ml). The extract was separated into acid and neutral fractions as described in paragraph a), and 67 mg of the acetoxy acid (II) and 45 mg of the acetoxy aldehyde (V) were obtained.

b) A solution of the oxide (I) (100 mg) in 5 ml of cyclohexane was treated with 25 ml of acetic acid and 200 mg of silica gel, and a mixture of ozone and oxygen was passed through the solution at 18-20°C until the ozone broke through. The solution was purged with nitrogen, the cyclohexane layer was decanted off, and the silica gel was washed with acetone. The cyclohexane and acetone solutions were combined, and the substance was hydrogenated over Lindlar catalyst (5 mg). The hydrogenation product was separated into acid and neutral fractions as

described in paragraph a). This 72 mg (64%) of the acetoxyaldehyde (V) and 31 mg (26%) of the acetoxy acid (II).

c) Experiment b) was repeated with the difference that 400 mg of silica gel was added to the solution. The results are given in Table 1.

Preparation of 8α-Acetoxybicyclohomofarnesan-12-oic Acid (II). a) The oxide (I) (100 mg) was ozonized as described above in the presence of silica gel, with the difference that 1 g of silica gel was added to the solution. The results are given in Table 1.

b) At −25 to −30°C, a current of ozonized oxygen was passed through a solution of 100 mg (0.38 mmole) of the oxide (I) in 7 ml of ethyl acetate until the ozone broke through. The solution was purged with nitrogen, left to warm up to 0°C, and diluted with 7 ml of acetone, and then a solution of 190 mg (1.9 mmole) of chromium trioxide in 0.2 ml of concentrated sulfuric acid was added dropwise and the mixture was stirred at 0°C for 2 h. After the addition of 20 ml of water to the reaction mixture, it was extracted with ether (3 × 20 ml) and the extract was washed with 1% KOH solution and with water and was dried and filtered, and the solvent was evaporated off to give 16 mg of neutral fraction. The alkaline extract was acidified with 10% H_2SO_4 and extracted with ether, and the extract was worked up in the usual way to give 76 mg of the acetoxy acid (II).

Preparation of Bicyclohomofarnesane-8α-12-diol (III). a) AT −65 to −70°C, a mixture of ozone and oxygen was passed through a solution of 100 mg of the oxide (I) in 10 ml of hexane until the ozone broke through. The residual ozone was displaced with nitrogen, the mixture was allowed to warm up to room temperature, the hexane was evaporated off in vacuum in a current of nitrogen, and the residue was dissolved in 5 ml of diethyl ether. After the addition of 28 mg of lithium tetrahydroaluminate to the solution, the mixture was boiled under reflux for 2 h. The excess of hydride was decomposed with ethyl acetate, and the mixture was worked up in the usual way, the neutral fraction being recrystallized from petroleum ether–diethyl ether (4:1). This gave 74 mg (76%) of bicyclohomofarnesane-8α,12-diol (III), mp 129-130°C, identified by comparison with an authentic sample.

b) The oxide (I) (100 mg; 0.38 mmole) was ozonized as described in paragraph a), the solvent was evaporated off at room temperature, the residue was dissolved in 1 ml of isopropanol, and the solution was added to a solution of lithium tetrahydroborate obtained as the result of the mixing at room temperature for 1 h of 146 mg (2.7 mmole) of potassium tetrahydroborate and 116 mg (2.7 mmole) of anhydrous lithium chloride in 4 ml of isopropanol. The mixture was stirred at 20°C for 30 min and at 60°C for 4 h, and then 3% of a 10% solution of caustic potash in isopropanol was added to it and the resulting mixture was stirred at 20°C for 30 min (monitoring by TLC). Then water was added and the products were extracted with ether (3 × 20 ml). The extract was washed with water, dried, and filtered, and the solvent was evaporated off in vacuum. This gave 86 mg of a neutral fraction and 19 mg of an acid fraciton. The neutral fraction was recrystallized from petroleum ether–diethyl ether (4:1) to give 59 mg of bicyclohomofarnesane-8α,12-diol (III), mp 129-130°C.

c) At −65 to −70°C, a mixture of ozone and oxygen was passed through a solution of 100 mg of the oxide (I) in 10 ml of isopropanol until the ozone broke through, and then the mixture was allowed to warm to room temperature and a solution of lithium tetrahydroborate prepared in the way described above from 147 mg of potassium tetrahydroborate and 116 mg of anhydrous lithium chloride was added to it. The reaction was carried out and the reaction mixture was worked up as described in paragraph b). In this way, 82 mg of neutral fraction and 9 mg of acid fraction were isolated. After recrystallization of the neutral fraction, 62 mg of the diol (III) was obtained with mp 129-130°C.

Preparation of 8α-Acetoxybicyclohomofarnesan-12-ol (VII). a) A solution of 100 mg (0.38 mmole) of the oxide (I) in 10 ml of methanol was saturated with ozone at −65 to −70°C and was allowed to warm to room temperature and was purged with nitrogen, and to the resulting solution was added a solution of lithium tetrahydroborate prepared in the way described above from 73 mg (1.35 mmole) of potassium tetrahydroborate and 57 mg (1.35 mmole) of anhydrous lithium chloride in 4 ml of isopropanol. The mixture was stirred at 20°C for 30 min and at 60°C for 4 h and was then acidified with 10 ml of 10% sulfuric acid and was extracted with ether. The extract was worked up in the usual way, giving 89 mg of a neutral fraction and 12 mg of an acid fraction. The first fraction was chromatographed on a column containing 3 g of silica gel, which led to the isolation of 70 mg (62%) of 8α-acetoxybicyclohomofarnesan-12-ol (VII), mp 84.5-85.5°C (from petroleum ether), $[\alpha]_D^{20}$ − 3.7° (c 2.1; $CHCl_3$). IR spectrum (cm^{-1})d: 1363, 1385

gem-dimethyl group); 1076, 3100-3600 (band with a maximum at 3450) (OH); 1240, 1727 (OAc). PMR spectrum (ppm): 0.77 (3H, s, CH_3 at C-10), 0.83 (3H, s), 0.85 (3H, s) [$C(CH_3)_2$]; 1.42 (3H, s, CH_3 at C-8); 1.88 (3H, s, CH_3CO), 3.45 (2H, t, J = 6 Hz, CH_2O). Found, %: C 73.10; H 11.09. $C_{18}H_{32}O_3$. Calculated, %: C 72.93; H 10.88.

b) At −65 to −70°C, a mixture of ozone and oxygen was passed through a solution of 100 mg of the oxide (I) in 10 ml of methanol until the ozone broke through. The ozone was displaced by nitrogen and the mixture was allowed to assume room temperature. Then 55 mg of KBH_4 was added to it and the resulting mixture was boiled under reflux for 2 h. After working up in the usual way, 81 mg of a neutral fraction and 15 mg of an acid fraction were obtained. Recrystallization of the neutral fraction from a mixture of petroleum ether and diethyl ether gave 60 mg (53%) of 8α-acetoxybicyclohomofarnesan-12-ol (VII), with mp 83-84°C.

LITERATURE CITED

1. P. F. Vlad and M. N. Koltsa, Synthesis and Use of Odoriferous Substances from Labdane Diterpenoids [in Russian], Shtiintsa, Kishinev (1988), p. 182.
2. L. Ruzicka, C. F. Seidel, and L. L. Engel, Helv. Chim. Acta, 25, No. 3, 621 (1942).
3. M. Hinder and M. Stoll, Helv. Chim. Acta, 33, No. 5, 1308 (1950).
4. R. C. Cambie, K. N. Joblin, and A. F. Preston, Aust. J. Chem., 25, No. 8, 1767 (1972).
5. I. C. Coste-Maniere, J. O. Zahra, and B. Waegell, Tetrahedron Lett., 29, No. 9, 1017 (1988).
6. M. Stoll and M. Hinder, Helv. Chim. Acta, 33, No. 5, 1251 (1950).
7. M. Stoll adn M. Hinder, Helv. Chim. Acta, 36, No. 7, 1984 (1953).
8. V. E. Sibirtseva, S. D. Kustova, V. Ya. Tokareva, P. F. Vlad, and M. N. Koltsa, Maslob-Zhir. Prom., No. 7, 29 (1980).
9. P. F. Vlad, A. N. Aryku, M. N. Koltsa, E. N. Shmidt, and V. A. Pentegova, Khim. Prir. Soedin., No. 4, 524 (1987).

SYNTHESIS OF (+)-DRIM-8-EN-11-OIC ACID

M. N. Koltsa, G. N. Mironov, and P. F. Vlad

UDC 547.597.595.1+542.91

A four-stage synthesis of (+)-drim-8-en-11-oic acid (IX) from norambreinolide (II) has been developed. The latter was converted by boiling with ethanolic sulfuric acid into a mixture of the methyl esters of bicyclohomofarnes-7- and -8-enoic acids which, on reaction with methyllithium, gave a mixture of 12-methyl-14,15,16-trinorlabd-7- and -8-en-12-ols. The alcohol with the Δ^8 double bond was dehydrated with p-toluenesulfonic acid to 11-methyl-14,15,16-trinorlabd-8,11-diene, the ozonization of which yielded (+)-drim-8-en-11-oic acid.

No few methods of synthesizing drimane sesquiterpenoids, among which there are valuable biologically active substances with various actions, have been described [1, 2]. The majority of these methods are multistage and inefficient; in addition, many of them lead to racemic products. The further search for convenient methods of obtaining the sesquiterpenoids therefore remains an urgent problem. Convenient starting compounds for the synthesis of drimane sesquiterpenoids are labdane diterpenoids, some of which are fairly readily available substances.

The aim of the present work was the synthesis of drim-8-en-11-oic acid (IX) from norambreinolide (II) – a product of the breakdown of sclareol (I) obtained industrially.

Institute of Chemistry, Academy of Sciences of the Moldavian SSR, Kishinev.

Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 214-221, March-April, 1991. Original article submitted April 12, 1990.