

Ozonolytic Decyclization of (*R*)-4-Menthen-3-one^{*,**}

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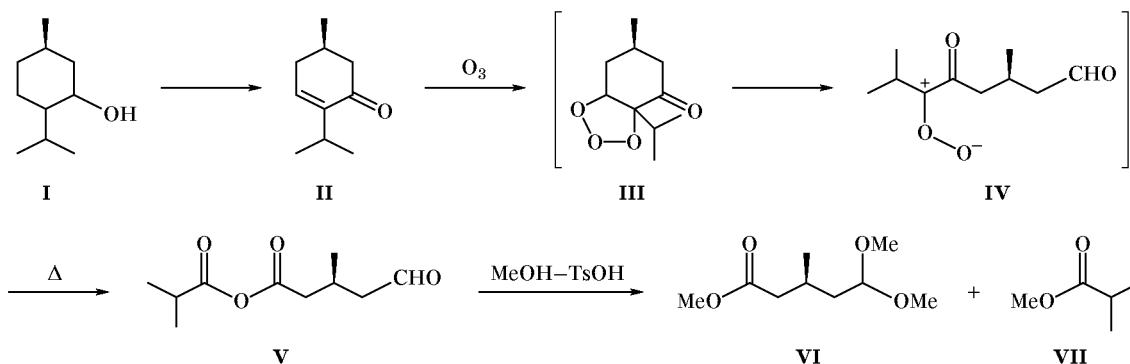
Abstract—Ozonolytic decyclization of (*R*)-4-menthen-3-one is accompanied by fragmentation of the isobutyl group, leading to ω -functionalized 3-methylpentanoic acid derivatives.

Monoterpenoids constitute a class of compounds which are widely used in the synthesis of optically active substances. One of such substrates is (*R*)-pulegone (enantiomeric purity 100%) which is isolated from *Mentha pulegium*. Numerous examples have been reported on the use of (*R*)-pulegone for the synthesis of chiral building blocks [2]. However, (*L*)-(-)-menthol (**I**), a relatively readily accessible monoterpene, has been reported mainly as a chiral auxiliary [3], whereas its application for the synthesis of chirons seems to be poorly explored. With the goal of further extending synthetic potential of (*L*)-(-)-menthol (**I**), in the present work we examined ozonolytic decyclization of (*R*)-4-menthen-3-one (**II**) which was obtained previously [4] from compound **I** via bromination–de bromination of the corresponding enol

acetate. Analysis of published data [5, 6] led us to presume that ozonolysis of the conjugated enone system in molecule **II** involves formation of zwitterionic intermediate **IV** through decomposition of ozonide **III**. If the ozonolysis is carried out in an inert medium, the subsequent rearrangement of intermediate **IV** (like the Baeyer–Villiger reaction [7, 8]) should give isobutyric (*3R*)-3-methyl-5-oxopentanoic anhydride (**V**). Acid methanolysis of mixed anhydride **V** should result in formation of the corresponding esters **VI** and **VII** (Scheme 1).

According to published data [7, 8], cleavage of the deactivated double bond in a conjugated enone system requires excess ozone. Therefore, we used 3.5 equiv of O₃ per mole of enone **II**. The reaction was carried out in methylene chloride at –65°C. The mixture was

Scheme 1.

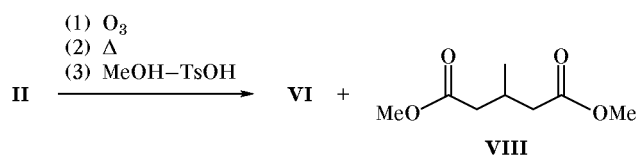


* For preliminary communication, see [1].

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then kept for 24 h at room temperature and treated with acidified methanol (method *a*) to isolate acetal **VI** and dimethyl 3-methylglutarate (**VIII**) (Scheme 2).

Scheme 2.

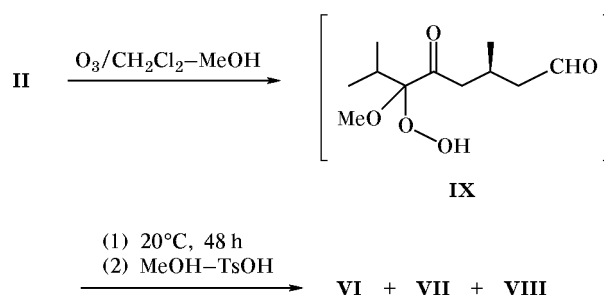


Taking into account that diester **VIII** could be formed by oxidation of the aldehyde group in **IV** during ozonolysis, the amount of ozone was reduced to 1 equiv. In this case, the conversion of enone **II** was also complete, but treatment of the reaction mixture according to procedure *a* gave a considerable amount of diester **VIII** (up to 10% with respect to **VI**). We succeeded in obtaining anhydride **V** by raising the reaction temperature to -20°C and using carbon tetrachloride as solvent instead of methylene chloride. The formation of compound **V** was confirmed by spectral data (which were obtained at room temperature). In the IR spectrum we observed absorption bands at 1720 and 2728 cm^{-1} , which are typical of aldehyde group, and anhydride carbonyl bands at 1808 and 1840 cm^{-1} . The aldehyde group in **V** gives rise to a multiplet at $\delta\ 9.77\text{ ppm}$ in the ¹H NMR spectrum and a doublet at $\delta_{\text{C}}\ 200.77\text{ ppm}$ in the ¹³C NMR spectrum. The anhydride carbonyl carbon atoms appear as singlets at $\delta_{\text{C}}\ 168.17$ and 172.30 ppm . No signals typical of ozonides were observed in the region $\delta_{\text{C}}\ 103\text{--}105\text{ ppm}$.

When ozonolysis of enones is performed at -65°C in methylene chloride [7] in the presence of methanol, zwitterionic intermediates are stabilized through transformation into α -methoxy hydroperoxides. Presumably, in our case (3*R*)-6-hydroperoxy-6-methoxy-3,7-dimethyl-5-oxooctanal (**IX**) is obtained. When the reaction mixture warms up to room temperature, compound **IX** decomposes with strong heat evolution, and the decomposition is complete in $\sim 48\text{ h}$ (according to the iodine-starch test). Methylation of the reaction mixture (method *b*) should give rise to acetal **VI** and volatile ester **VII** (Scheme 3). However, even with 0.85 equiv of ozone per mole of enone **II**, the reaction mixture contained diester **VIII** together with compound **VI** (according to the GLC data; see table). Probably, the aldehyde group in **IX** is oxidized by the hydroperoxide moiety either intra- or intermolecularly. When the reaction mixture was treated with methanol immediately after ozonolysis (method *c*), only traces of diester **VIII** were formed. Obviously,

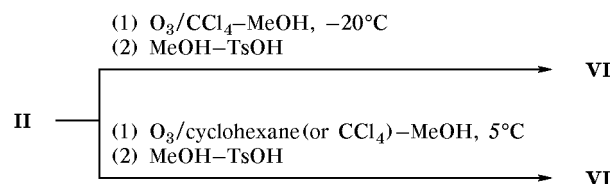
in this case the aldehyde group is protected via acetalization.

Scheme 3.



The oxidation of **II** with 1 equiv of ozone in carbon tetrachloride at -20°C in the presence of 2 equiv of methanol and the subsequent methylation (method *c*) led to formation of acetal **VI**. The same result was obtained on raising the temperature to 5°C . At that temperature the reaction may be performed in cyclohexane in the presence of methanol with the same amount of ozone (Scheme 4). It should be noted that in the ozonolysis in carbon tetrachloride and cyclohexane in the presence of methanol the reaction mixture divided into layers.

Scheme 4.



GLC analysis of the methylation products obtained according to method *c* (0.85 mol of O₃, 1 mol of enone **II**, methanol) showed the presence of a considerable amount of diester **VIII** in addition to initial enone **II** and acetal **VI**. This may be due to better solubility of hydroperoxide **IX** in methanol than in nonpolar solvents, so that the aldehyde moiety in **IX** can be oxidized to carboxy group with an ozone-oxygen mixture.

Our experimental data indicate enhanced reactivity of the double bond in enone **II** in the ozonolysis. Presumably, positive inductive effect of the isopropyl group partially compensates negative mesomeric effect of the carbonyl group in menthenone **II**, which favors delocalization of the double bond intrinsic to common enone systems. For example, the ozonolysis of 1-methylcyclohexene in methanol at -40°C is complete on passing 1 equiv of ozone [9], whereas

Ozonolysis of (*R*)-4-menthen-3-one

Run no. ^a	Amount of O ₃ , mol per mole of II	Solvent	Temperature, °C	Decomposition method ^b	Products
1	3.5	CH ₂ Cl ₂	-65	<i>a</i>	VI, VIII
2	1	CH ₂ Cl ₂	-65	<i>a</i>	VI, VIII
3	1	CCl ₄	-20	Without decomposition	V
4	0.85	CH ₂ Cl ₂ -MeOH	-65	<i>b</i>	II, VI, VIII
5	1	CH ₂ Cl ₂ -MeOH	-65	<i>c</i>	VI, VIII
6	1	CCl ₄ -MeOH	-20	<i>c</i>	VI
7	1	CCl ₄ -MeOH	5	<i>c</i>	VI
8	1	<i>cyclo</i> -C ₆ H ₁₂ -MeOH	5	<i>c</i>	VI
9	0.85	MeOH	5	<i>c</i>	II, VI, VIII

^a See Experimental.

^b Method *a*: methanolysis after 24 h; *b*: methanolysis after 48 h; *c*: methanolysis immediately after ozonolysis.

3 to 12 equiv of ozone is required to effect ozonolysis of 2-cyclohexenone.

The stability of peroxy-containing ozonolysis products increases as the solvent polarity rises, i.e., in going from carbon tetrachloride to methylene chloride and then to methanol. Zwitterionic intermediate **IV** is likely to form a relatively stable complex with methylene chloride whose dipole moment is about 1.6 D, and peroxide products decompose within 24 h. In carbon tetrachloride ($\mu = 0$), the rate of rearrangement of analogous complex is considerably higher, and the reaction yields anhydride **V**. As stated above, stabilization of intermediate **IV** in methanol is achieved via formation of even more stable α -methoxy hydroperoxide **IX**.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples prepared as thin films. The ¹H and ¹³C NMR spectra were obtained on a Bruker AMX-300 instrument (300.13 MHz for ¹H and 75.47 MHz for ¹³C) using CDCl₃ as solvent and internal reference (δ 7.27 ppm, δ_C 77.00 ppm). GLC analysis was performed on a Chrom-5 chromatograph; 1.2-m column packed with 5% of SE-30 on Chromaton N-AW-DMCS (0.16–0.20 mm); oven temperature 50–300°C; carrier gas helium. The specific rotations were measured on a Perkin-Elmer-241-MC instrument. The reactions were carried out in dry purified solvents. The ozonizer efficiency was 40 mmol of O₃ per hour. The presence of peroxide compounds was checked by iodine-starch test.

Ozonolysis of (*R*)-4-menthen-3-one. *Run no. 1.* An ozone-oxygen mixture (3.5 equiv of O₃ with

respect to **II**) was passed at -65°C through a solution of 1.00 g (6.58 mmol) of enone **II** in 10 ml of CH₂Cl₂. The mixture was then treated according to method *a*: it was purged with argon and was left to stand for 24 h at room temperature; a solution of 0.05 g of *p*-toluenesulfonic acid in 20 ml of methanol was added, the mixture was stirred for 48 h, 0.50 g of NaHCO₃ was added, and the mixture was evaporated under reduced pressure. The residue was treated with 50 ml of Et₂O, and the extract was washed with a saturated solution of NaCl (to pH 7), dried over Na₂SO₄, and evaporated to obtain 1.12 g of an oily substance which contained mainly (according to the GLC data) compounds **VI** and **VIII** at a ratio of 7:3. By chromatography on silica gel [gradient elution with petroleum ether (bp 40–70°C)-*tert*-butyl methyl ether, 10:1 to 3:1] we isolated 0.21 g (16.8%) of acetal **VI** and 0.43 g (37.8%) of diester **VIII**.

Run no. 2. An ozone-oxygen mixture (1 equiv of O₃) was passed at -65°C through a solution of 1.00 g (6.58 mmol) of enone **II** in 10 ml of CH₂Cl₂. The mixture was then treated according to procedure *a* to obtain 1.21 g of an oily substance. The major components of the product were compounds **VI** and **VIII** at a ratio of 9:1 (GLC).

Run no. 3. An ozone-oxygen mixture (1 equiv of O₃) was passed at -20°C through a solution of 0.20 g (1.31 mmol) of enone **II** in 11 ml of CCl₄. The mixture was concentrated by purging with argon. According to the spectral data, the residue contained anhydride **V**. IR spectrum, ν , cm⁻¹: 808, 936, 1080, 1168, 1232, 1288, 1412, 1456, 1504, 1520, 1680, 1704, 1720, 1740, 1808, 2728, 3050. ¹H NMR spectrum, δ , ppm: 1.10 d (3H, 3-CH₃, *J* = 8.9 Hz), 1.23 d (6H, 2'-CH₃, *J* = 7.0 Hz), 2.32–2.72 m (6H, CH₂,

CH), 9.77 d (1H, CHO, $J = 0.005$ Hz). ^{13}C NMR spectrum, δ_{C} , ppm: 18.23 ($\text{C}^{2'}$), 19.79 (3- CH_3), 24.64 (C^3), 34.92 (2'- CH_3), 41.42 (C^2), 49.60 (C^4), 168.17 (C^1), 172.30 (C^1), 200.77 (CHO).

Run no. 4. An ozone–oxygen mixture (0.85 equiv of O_3) was passed at -65°C through a solution of 1.00 g (6.58 mmol) of enone **II** in 10 ml of CH_2Cl_2 containing 0.54 ml (0.43 g, 13.4 mmol) of methanol. The mixture was treated according to procedure *b*: it was purged with argon and was left to stand for 48 h at room temperature. A solution of 0.05 g of *p*-toluenesulfonic acid in 20 ml of methanol was added, the mixture was stirred for 48 h, 0.50 g of NaHCO_3 was added, and the mixture was evaporated under reduced pressure. The residue was treated with 50 ml of Et_2O , and the extract was washed with a saturated solution of NaCl (to pH ~ 7), dried over Na_2SO_4 , and evaporated. The residue was 1.05 g of an oily substance which contained mainly compounds **II**, **VI**, and **VIII** at a ratio of 1:3:2 (GLC).

Run no. 5. An ozone–oxygen mixture (1 equiv of O_3) was passed at -65°C through a solution of 1.00 g (6.58 mmol) of enone **II** in 10 ml of CH_2Cl_2 containing 0.54 ml (0.43 g, 13.4 mmol) of methanol. The mixture was treated according to procedure *c*: it was purged with argon, a solution of 0.05 g of *p*-toluenesulfonic acid in 20 ml of methanol was added, the mixture was stirred for 48 h, 0.50 g of NaHCO_3 was added, and the mixture was evaporated under reduced pressure. The residue was treated with 50 ml of Et_2O , and the extract was washed with a saturated solution of NaCl (to pH ~ 7), dried over Na_2SO_4 , and evaporated under reduced pressure. The residue was 1.15 g of an oily substance, the major component of which was acetal **VI** (GLC).

Run no. 6. An ozone–oxygen mixture (1 equiv of O_3) was passed at -20°C through a solution of 1.00 g (6.58 mmol) of enone **II** in 7 ml of CCl_4 containing 0.54 ml (0.43 g, 13.4 mmol) of methanol. The mixture was then treated according to procedure *c* to obtain 1.06 g (85%) of acetal **VI**.

Run no. 7. An ozone–oxygen mixture (1 equiv of O_3) was bubbled at 5°C through a solution of 5.00 g (32.9 mmol) of enone **II** in 35 ml of CCl_4 containing 2.82 ml (65.9 mmol) of methanol. The mixture was purged with argon, a solution of 0.25 g of *p*-toluenesulfonic acid in 50 ml of methanol was added, and the mixture was left to stand for 2 days at room temperature (until peroxide compounds disappeared according to iodine–starch test). Sodium hydrogen carbonate, 2.50 g, was added, and the mixture was evaporated under reduced pressure. The residue was treated with 100 ml of Et_2O , and the extract was washed with a saturated solution of sodium chloride

(to pH ~ 7), dried over Na_2SO_4 , and evaporated to obtain 5.44 g (87%) of acetal **VI**.

Run no. 8. An analogous experiment was carried out in cyclohexane.

Run no. 9. An ozone–oxygen mixture (0.85 1 equiv of O_3) was passed at 5°C through a solution of 1.00 g (6.58 mmol) of enone **II** in 10 ml of methanol. The mixture was then treated according to procedure *c* to isolate 1.20 g of an oily substance. According to the GLC data, the major components of the product were compounds **II**, **VI**, and **VIII** at a ratio of 2:2:1.

Methyl (R)-5,5-dimethoxy-3-methylpentanoate (VI). $[\alpha]_{\text{D}}^{25} = -1.54^\circ$ ($c = 4.76$, CHCl_3) (cf. [10]). The IR and ^1H NMR parameters were almost identical to those reported in [10]. ^{13}C NMR spectrum, δ_{C} , ppm: 19.48 q (3- CH_3); 26.14 d (C^3); 38.38 t (C^4); 40.78 t (C^2); 50.56 q, 51.42 q, and 52.00 q (OCH_3); 102.30 d (C^5), 172.35 s (C^1).

Dimethyl 3-methylglutarate (VIII). The IR and ^1H NMR spectral parameters were almost identical to those reported in [11].

REFERENCES

1. Kharisov, R.Ya., Botsman, O.V., Gazetdinov, R.R., Ishmuratov, G.Yu., and Tolstikov, G.A., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2001, no. 6, p. 1067.
2. Ishmuratov, G.Yu., Yakovleva, M.P., Kharisov, R.Ya., and Tolstikov, G.A., *Monoterpenoidy v sinteze opticheski aktivnykh feromonov nasekomykh* (Monoterpenoids in the Synthesis of Optically Active Insect Pheromones), Ufa: Gilem, 1999.
3. Weiping, C. and Jianliang, X., *Tetrahedron Lett.*, 2001, vol. 42, pp. 2897–2899.
4. Treibs, W. and Albrecht, H., *J. Prakt. Chem.*, 1961, vol. 13, nos. 5–6, pp. 291–305.
5. Fliszar, S. and Granger, M., *J. Am. Chem. Soc.*, 1969, vol. 91, no. 12, pp. 3330–3337.
6. Odinokov, V.N. and Tolstikov, G.A., *Usp. Khim.*, 1981, vol. 50, no. 7, pp. 1207–1251.
7. Chorvat, R.J. and Pappo, R., *J. Org. Chem.*, 1976, vol. 41, no. 17, pp. 2864–2865.
8. US Patent no. 3 109 016, 1963; *Chem. Abstr.*, 1964, vol. 60, p. 3045 f.
9. Galin, F.Z., Kukovinets, O.S., Zainullin, R.A., Shreshovets, V.V., Kashina, Yu.A., Akhmetov, A.M., Kunakova, R.V., and Tolstikov, G.A., *Russ. J. Org. Chem.*, 2001, vol. 37, no. 2, pp. 238–242.
10. Mori, K. and Kuwahara, S., *Tetrahedron*, 1982, vol. 38, no. 4, pp. 521–525.
11. Lam Lister, K.P., Hui Raimond, A.H.F., and Jones, J.B., *J. Org. Chem.*, 1986, vol. 11, no. 11, pp. 2047–2050.