New Approach to the Synthesis of Pheromones and Juvenoids with Small Rings in the Molecule

O. S. KUKOVINETS[1], T. I. ZVEREVA[1], V. G. KASRADZE[2], M. I. ABDULLINA[1] and G. A. TOLSTIKOV[3]

[1]*Bashkiria State University, Ul. Zaki-Validi 32, Ufa 450074 (Russia)*

E-mail: kukovinets@mail.ru

[2]*Institute of Organic Chemistry, Ufa Scientific Centre of the Russian Academy of Sciences, Pr. Oktyabrya 71, Ufa 450054 (Russia)*

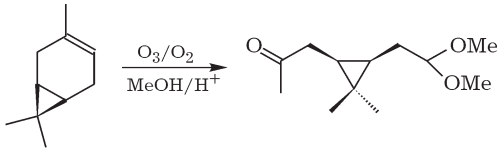
[3]*Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Pr. Akademika Lavrentyeva 9, Novosibirsk 630090 (Russia)*

Abstract

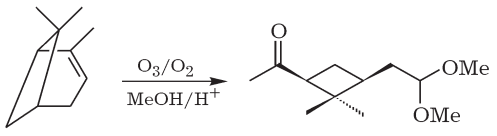
Naturally occurring terpenes such as (+)-3-carene and α-pinene find a wide application in the synthesis of biologically active substances. Basing on the products of their ozonolytic decomposition reaction schemes have been developed for the synthesis of juvenoids, pheromones, pyrethroids. The present paper is devoted to proposing a new efficient approach to the synthesis of pheromones and juvenoids with cyclopropane and cyclobutane ring in the molecule via ozonization of α,β-unsaturated ketones such as carenone and verbenone, easily obtained from (+)-3-carene and α-pinene. A mechanism is suggested for the formation of 2,2-dimethyl-3-acetylcyclobutane carbonic acid, the synton in the synthesis of citrus mealybug pheromone.

Key words: (+)-3-carene, α-pinene, ozonolysis, pheromones, juvenoids, biologically active compounds

Synthetic and naturally occurring isoprenoids and terpenoids find a wide application in the synthesis of biologically active compounds including juvenoids and pheromones. A considerable role in this field is played by (+)-3-carene **1** and α-pinene **2**, whose ozonolytic decomposition results in the formation cyclobutane and cyclopropane derivatives with definite stereochemistry of optically active centres. The latter have oxygen-containing functional groups with a differentiated reactivity [1].



(1*S*, 3*R*)–**1** (1*R*, 3*S*)–**3**

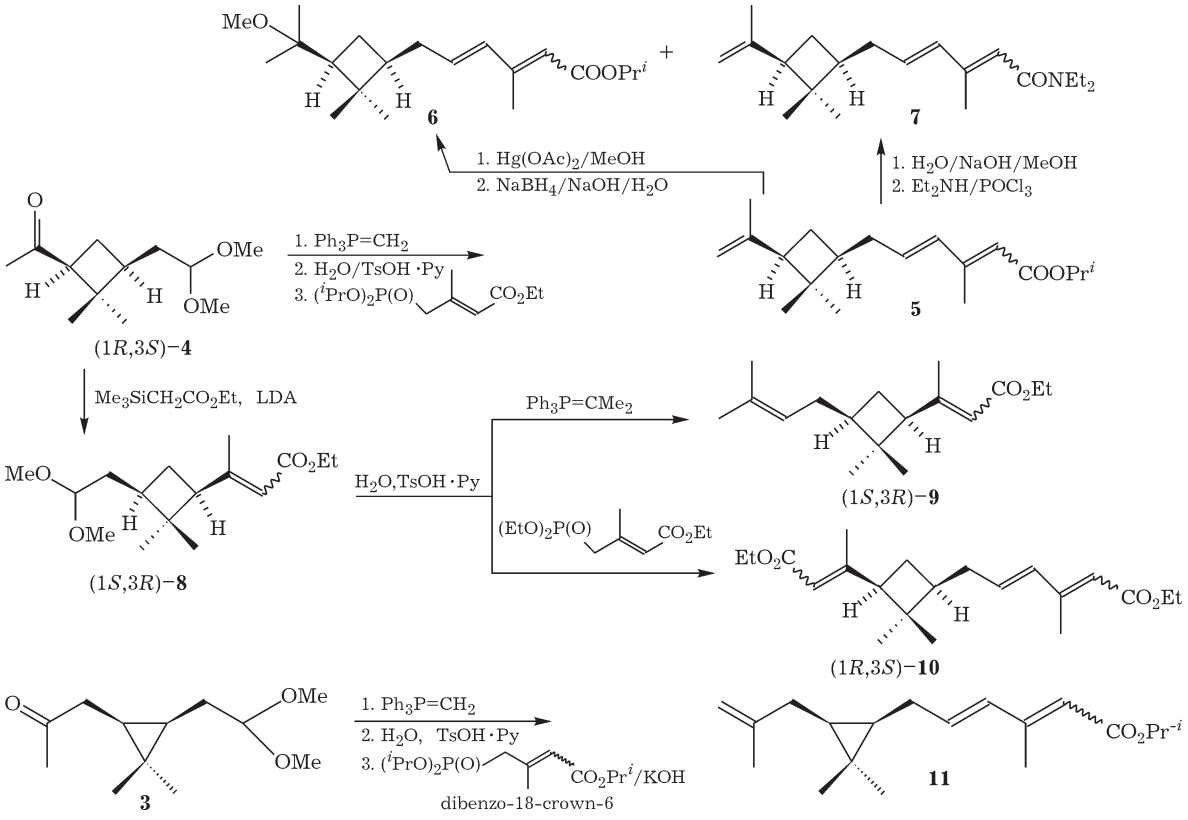


(1*R*, 5*R*)–**2** (1*S*, 3*R*)–**4**

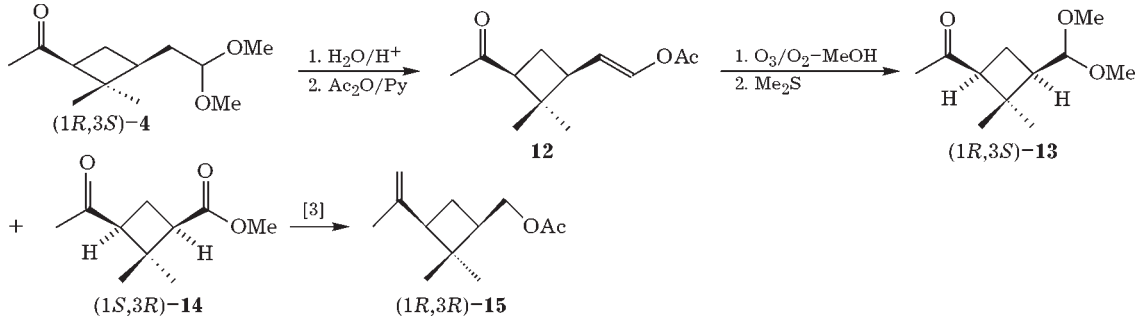
For example, compounds **3** and **4** obtained from (+)-3-carene and α-pinene were used in the synthesis of the analogues of juvenile hormones containing 2,4-diene system and three- or four-membered cycle in the molecule [2] (Scheme 1).

Basing on ketoacetal **4** we have performed the synthesis of the pheromone of the citrus mealybug [3]. This method is characterized by stereoselectivity, however the stages of ketoacetal **4** conversion into enolacetate **12** and its subsequent ozonization occur with a low yield, which results in reducing the total yield of pheromone **15** (Scheme 2).

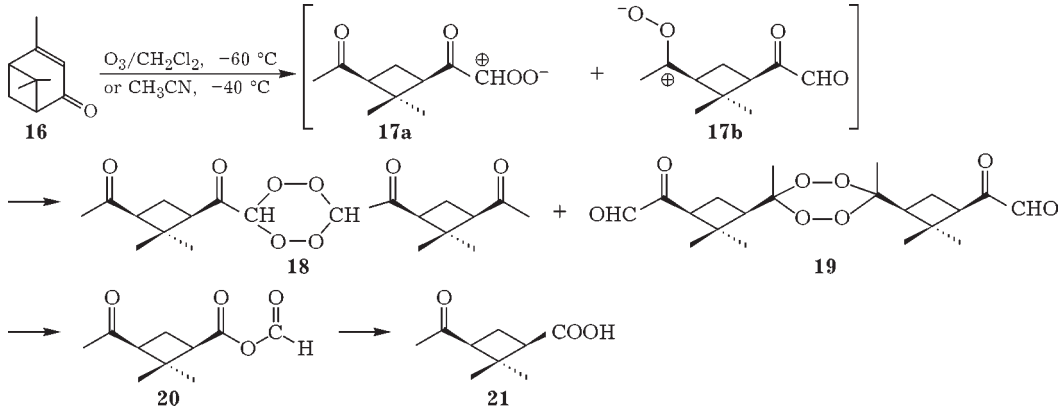
We have revealed that it would be more efficient to carry out preliminary liquid-phase oxidation of α-pinene **2** to produce verbenone **16**, whose subsequent ozonolysis in acetonitrile medium (at −40 °C) or in CH_2Cl_2 medium (at −60 °C) occurs in a stereo- and chemoselective fashion through the stages of formed zwitterions **17a** and **17b** dimerization to give dimeric peroxides **18** and **19**. On heating up to a room



Scheme 1.



Scheme 2.



Scheme 3.

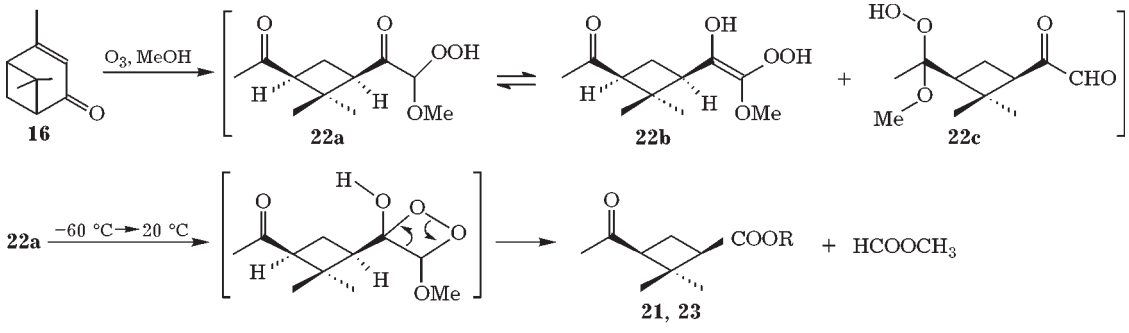
temperature the latter undergo rearrangement through the mixed anhydride **20** to yield ketoacid **21**, the precursor of pheromone **15** (Scheme 3).

The fact of dimeric peroxide formation at −60 and −40 °C and their rearrangement to yield mixed anhydride **20** at 20 °C is confirmed by NMR spectral data for compounds **18** and **19** obtained at a lowered temperature immediately after the ozonization, as well as their changes with rising the temperature value up to a room temperature (NMR spectra parameters in this case are corresponding to anhydride **20**).

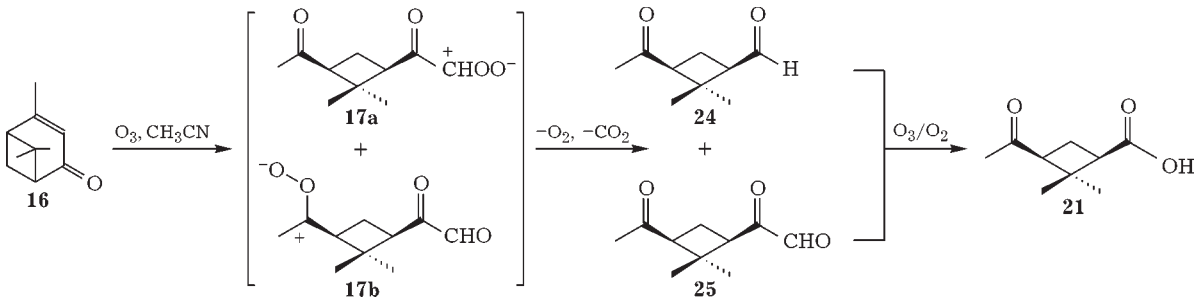
The quantitative determination of peroxides in the products of verbenone **16** ozonization in a methanol medium at various temperature values has demonstrated that with the rise in temperature, as well as with the ozonization in aprotic solvents one can observe their spontaneous decomposition to occur which is not requiring for the action of a reducer. In the course of time, ketoacid **21** is gradually crystallized from the solution. To all appearance, as the temperature rising, the equilibrium is displaced in the direction of methoxyhydroperoxide **22a** that undergoes rearrangement with the formation of acid **21**. The partial methylation of this acid during the reaction resulting in the formation of ester **23** could be confirmed by the presence of an absorption band at 1745 cm^{-1} in the IR spectrum of the overall product as well as of a signal at 3.67 ppm in ^1H NMR spectrum. Ester **23** separated from acid **21** by means of column chromatography was identified with the use of a GLC technique (the label of a known sample) as well as using NMR spectral data. Methyl formate produced due to the rearrangement was identified with the help of a capillary chromatography (Scheme 4).

In other way an "abnormal" ozonolysis of verbenone **16** in acetonitrile medium at −20...0 °C occurs. The formed zwitterions **17a**, **b** decompose to produce compounds **24** and **25**, whose aldehyde group is rapidly oxidized with the ozone-oxygen mixture to yield ketoacid **21** (Scheme 5).

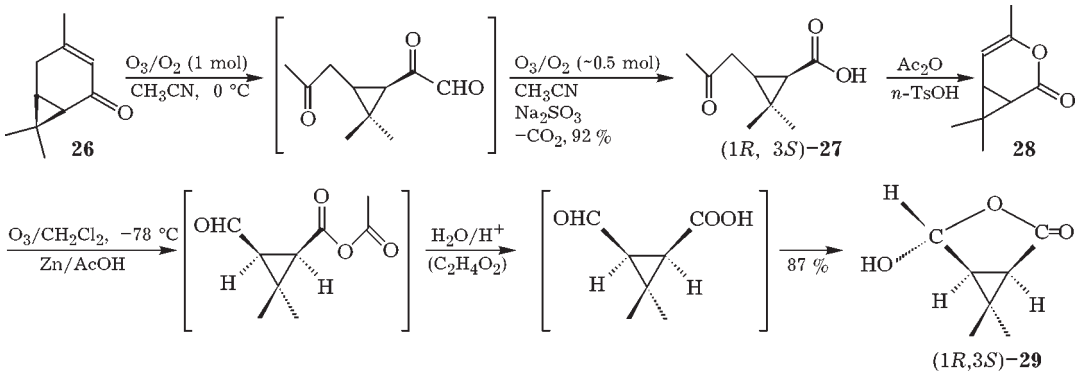
Thus, with the use of verbenone as an initial compound one could carry out the synthesis of citrus mealybug pheromone **15** without reduction of peroxide products of ozonolysis those undergo a spontaneous rearrangement to give ketoacid **21**. The total yield of pheromone **15** is 43 % increased [4] in comparison with the yield of this compound in case that the method described in [1] is used.



Scheme 4.



Scheme 5.



Scheme 6.

The ozonolysis features revealed have appeared general ones for bicyclic α,β-unsaturated ketones, which was demonstrated by the example of carenone **26** ozonolysis. The ozonolytic cleavage of double bond in the bicycle is also accompanied with an additional cleavage of a neighboring y-bond and with the formation of ketoacid **27** that serves as a precursor of lactol **29**, an intermediate species in many syntheses of biologically active compounds [5] (Scheme 6).

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