

Controlled Ozonolysis of Alkenes

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Abstract

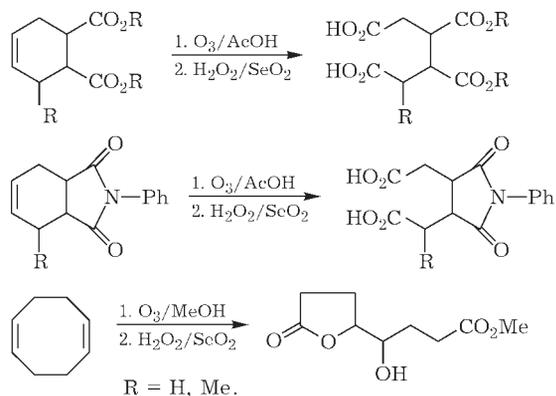
Polyfunctional aliphatic and heterocyclic compounds, as well as α,ω -bifunctional unsaturated compounds with required (*Z*) or (*E*) configuration have been synthesized using controlled ozonolysis of acyclic, cyclic and bicyclic alkenes and polyenes of regular structure and preset configuration *via* dosing a calculated amount of ozone and the subsequent controlled decomposition of peroxide products resulted from ozonolysis. Transformation pathways are proposed for ozonolysis products in the synthesis of insect pheromones, juvenoids, acyclic terpenoids, tocopherols, ecdysteroids and their analogues.

Key words: ozonolysis, controlled, alkenes, polyenes, cyclic, bicyclic, unvulcanized rubbers, pheromones, juvenoids, polyprenols, terpenoids, chlorophyll, phyton, α -tocopherol, ecdysteroids, analogues

Ozonolysis as a recognized method for establishing the location of a double bond in non-saturated compounds has become an important technique of synthetic organic chemistry within 1960–1970ths. Methods and expedients were developed for the ozonolysis of alkenes in order to obtain carbonic acids, aldehydes, ketones, alcohols [1–4].

An oxidative decomposition stage (as a rule, under the action of hydrogenperoxide) of peroxide products formed due to ozonization is of an important value in the synthesis of carbonic acids based on the ozonolysis of alkenes. We have developed a method for catalyzing the process with the help of selenium dioxide [5] which allows researchers to convert selectively alkenes and polyenes with labile functional groups into target aliphatic and heterocyclic polyfunctional compounds (polycarbonic acids and their acidic esters, pyrrolidine-2,5-diones, dihydroxy substituted α,ω -dicarbonic acids [6–9] (Scheme 1).

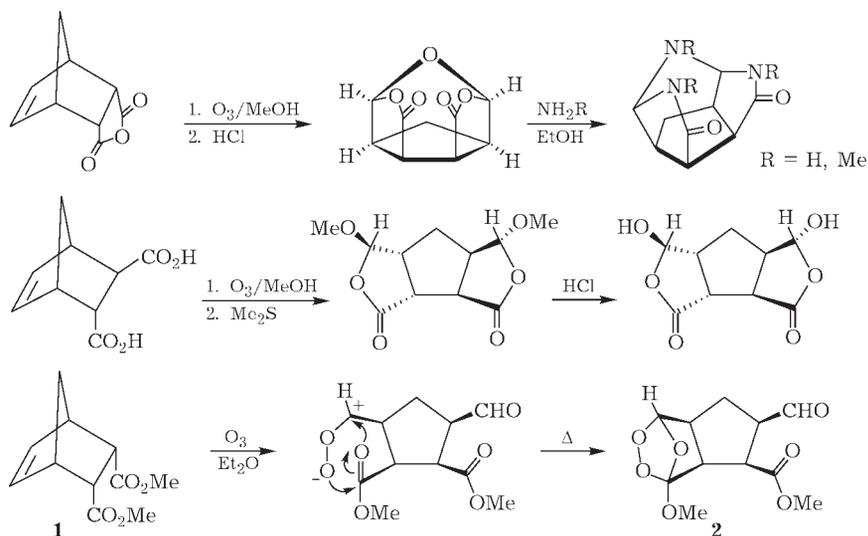
With the use of structural and stereochemical features of intermediate species formed under the ozonolysis of bicyclic carboxyalkenes an original approach was proposed with respect to the stereochemically controlled synthesis of polyfunctional oxygen- and nitrogen-containing heterocyclic compounds [10, 11] (Scheme 2).



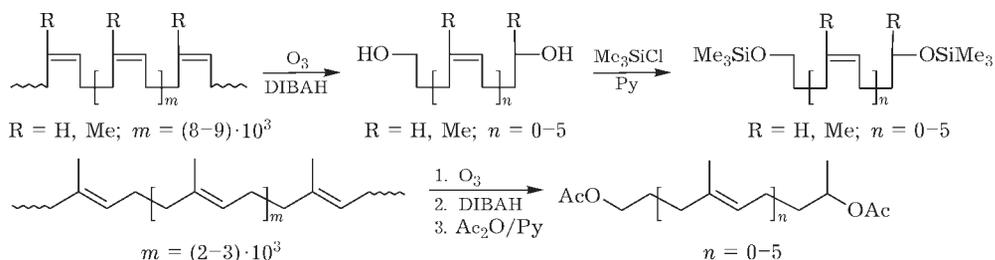
Scheme 1.

Using the ozonization of dimethyl ester of endo-,*cis*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid **1** in diethyl ether we pioneered the synthesis of crystalline α -methoxyozonide **2** (m. p. being of 111–112 °C) whose structure has been supported by XRD data [12] (see Scheme 2). The formation of methoxyozonide could be caused by the fact that a bipolar ion generated under ozonolysis is involved in the intramolecular interaction preferably with the vicinal ester group rather than with a remote, though a much more reactive aldehyde group.

In the studies on the ozonolysis of unvulcanized rubbers we revealed that under dosing



Scheme 2.



Scheme 3.

of 40 % amount of ozone with respect to equimolar ratio (as calculated for an isoprene link natural unvulcanized rubber or synthetic one such as SKI-3) a low-molecular fraction ($M \sim 3000$) of (*Z*)-1,4-oligoisoprene- α,ω -glycols is formed with the yield of 60 % in non-polar solvent (benzene, CH_2Cl_2) in the presence of methanol [13]. According to data of the GLC analysis of their bis-(trimethylsilyl) ethers, this fraction of α,ω -diols represents a mixture of isoprenologs (Fig. 1).

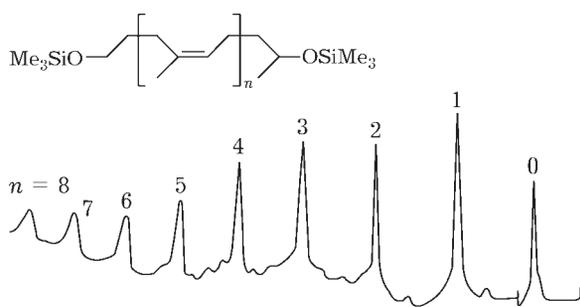
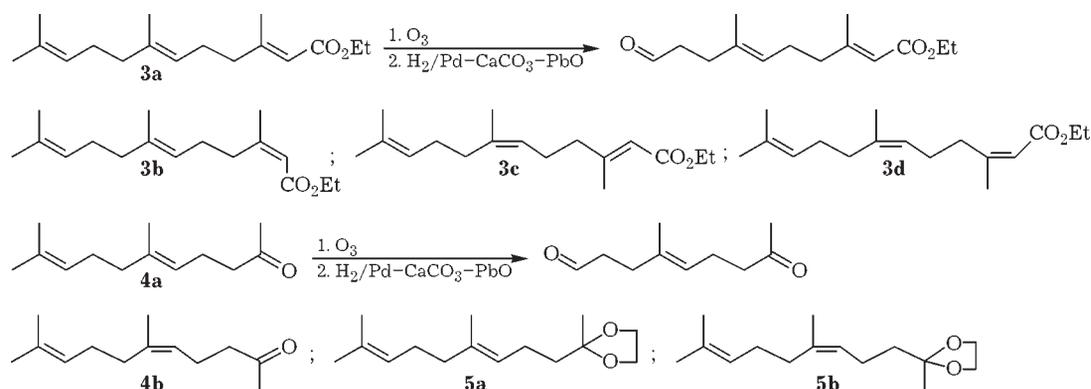


Fig. 1. Data of GLC analysis of bis(trimethylsilyl) ethers of (*Z*)-1,4-oligoisoprene- α,ω -glycols.

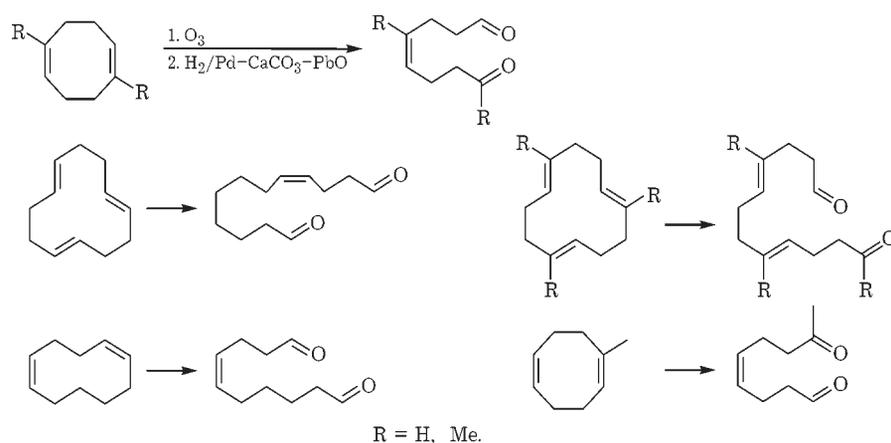
A high-vacuum distillation of the mixtures of trimethylsilyl ethers or bis-acetates of oligomeric α,ω -glycols obtained by the partial ozonolysis of (*E*)-1,4-polyisoprene, (*E*)-1,4-polyisoprene (gutta-percha) and (*Z*)-1,4-polybutadiene results in the formation of corresponding individual (*Z*)- and (*E*)-polyene α,ω -diols with the number of monomeric links $n = 1-5$ (Scheme 3) [14-18]. Some from these compounds ($n = 1$ and 2) have been used in the synthesis of pheromones.

Blocks for acyclic polyisoprenoids [19] have been synthesized, criteria for establishing their configuration using the method of ^{13}C NMR spectroscopy have been revealed [20], octa- and nonaprenoles have been synthesized [21].

The controlled partial ozonolysis of polyunsaturated acyclic and cyclic compounds has offered a novel efficient pathway for the synthesis of hard-to obtain α,ω -bifunctional compounds containing double bonds with preset (*Z*) or (*E*) configuration [22].



Scheme 4.



Scheme 5.

The potentialities of the controlled ozonolysis of acyclic polyenes were demonstrated by the example of stereoisomeric farnesyl esters **3a-d**, geranyl- and nerylacetonones **4a,b**, and their derivatives **5a,b**. A regiodirectionality has been established for the ozonolysis of terminal isopropylidene groups in linear isoprenoid compounds (Scheme 4) [23].

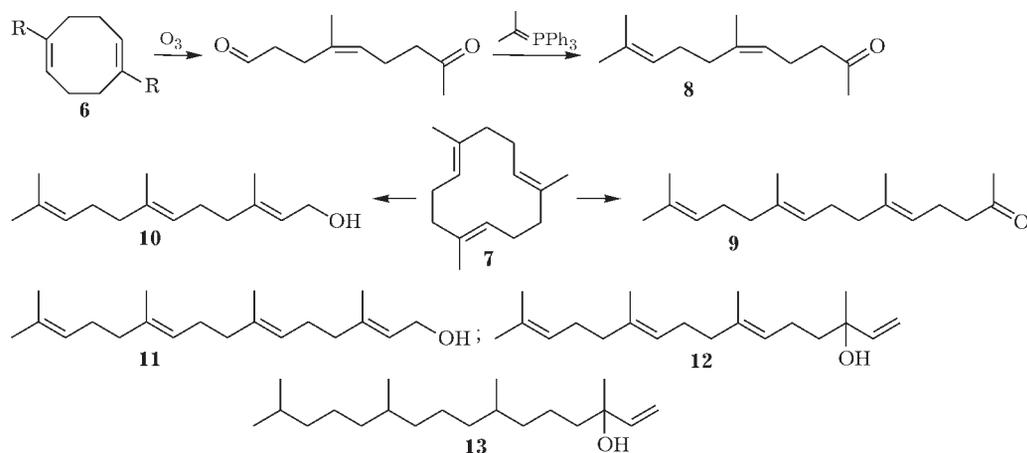
The controlled ozonolysis of one of multiple bonds in cyclic oligomers of conjugated dienes has offered broad potentials for applying the synthesis of α,ω -bifunctional alkenes and dienes with a preset configuration. Dimers and trimers of isoprene and butadiene as well as their co-oligomers have been involved in the partial ozonolysis (Scheme 5) [24]. For the first time it has been established, that (*E*) bond can be selectively ozonized in cyclic polyenes containing double bonds with (*Z*) or (*E*) configuration. In case that the molecule of cyclooligomer contains di- and trisubstituted double bonds, a more

substituted double bond [25] is preferably subjected to attack by ozone.

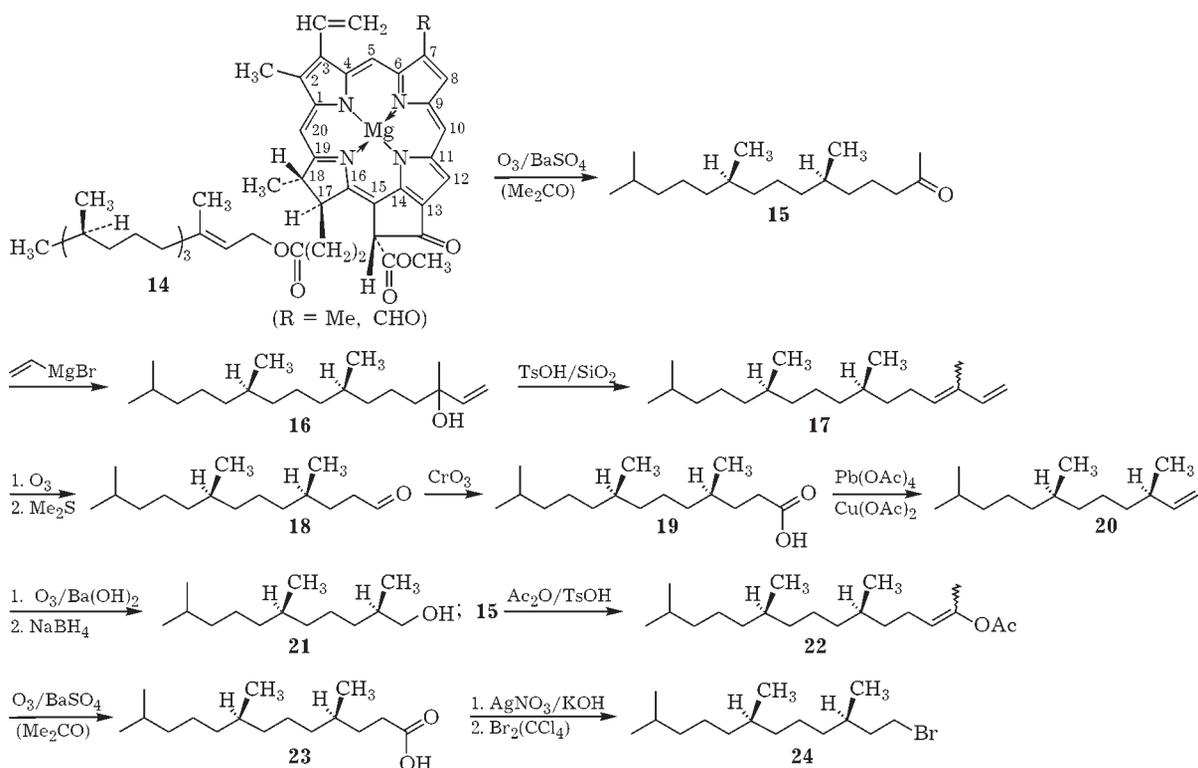
Basing on controlled ozonolysis of (*Z,Z*)-1,5-dimethyl-1,5-cyclooctadiene **6** and (*E,E,E*)-1,5,9-trimethyl-1,5,9-cyclododecatriene **7** a new approach to the synthesis of acyclic (*Z*)- and (*E*)-1,5-polyene isoprenoids, insect feromones, juvenoids [26, 27] has been developed. (*Z*)-geranyl- and (*E,E*)-farnesylacetones (**8** and **9**, respectively) [28], (*E,E*)-farnesol **10** and (*E,E,E*)-geranylgeraniol **11** [29], (*E,E*)-geranylinalool **12** and isophytol **13** [30] have been synthesized (Scheme 6).

The controlled ozonolysis of butadiene oligomers and its co-oligomers with isoprene has become a basis for the synthesis of pheromones belonging to the acetogenine series [31].

Ozonolysis is finding an increasing application in the chemistry of low-molecular bioregulators [32]. Chiral isoprenoid C_{14} , C_{15} и C_{16} syntons with (*R,R*)-configuration are required in the convergent synthesis of optically active



Scheme 6.



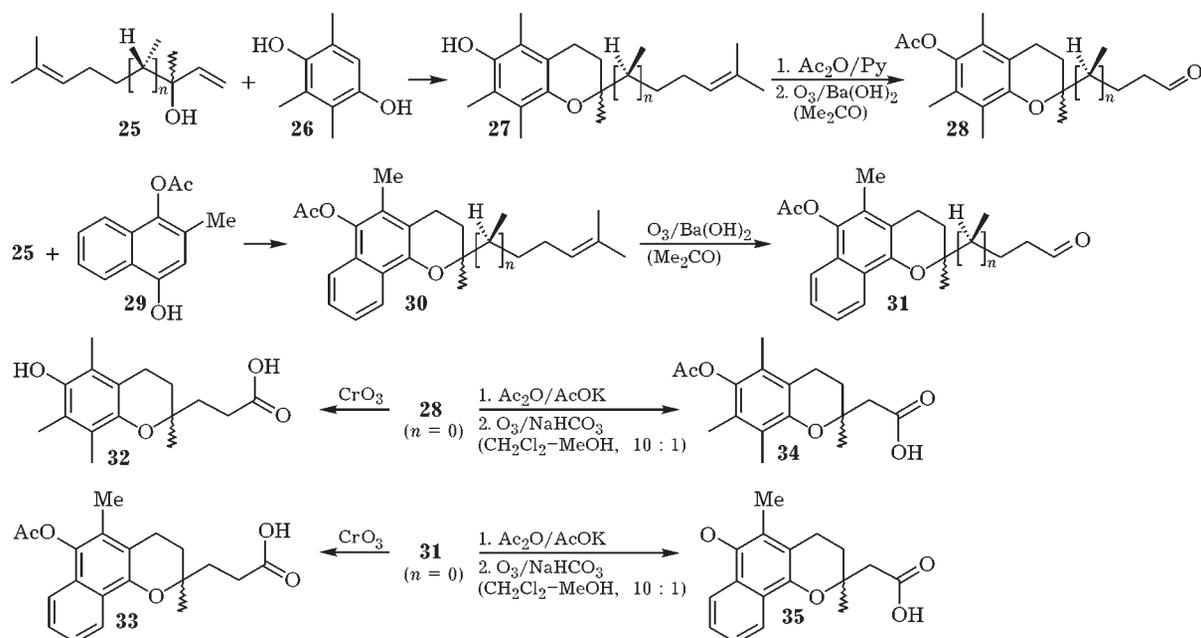
Scheme 7.

α -tocopherol with natural (*R,R,R*)-configuration – the main component of vitamin E – for the construction of a side chain. We have proposed to synthesize these species basing on ozonolysis of chlorophyll 14 in acetone extract from the stinging nettle (*Urtica dioica*) [33] (Scheme 7).

Ozonolysis was repeatedly applied for the subsequent transformations (*R,R*)-phyton 15 obtained from chlorophyll. After the conversion of the phyton into (*7R,11R*)-isophytol 16 and the further acid catalyzed dehydration the mixture of (*E*)- and (*Z*)-1,3-phytadienes 17 ob-

tained was subjected to ozonolysis to obtain C_{16} -aldehyde 18. The oxidation of the latter to yield acid 19, its oxidative decarboxylation and the subsequent ozonolysis of alkene 20 resulted in the formation of C_{14} -alcohol 21 [34] (see Scheme 7). The ozonization of enoacetate 22 with a double molar excess of ozone resulted in the obtaining of acid 23 which has been converted into hexahydrofarnesyl bromide 24 *via* Hunsdiecker reaction [35] (see Scheme 7).

With the use of chlorophyll ozonolysis product we have been synthesized optically active



Scheme 8.

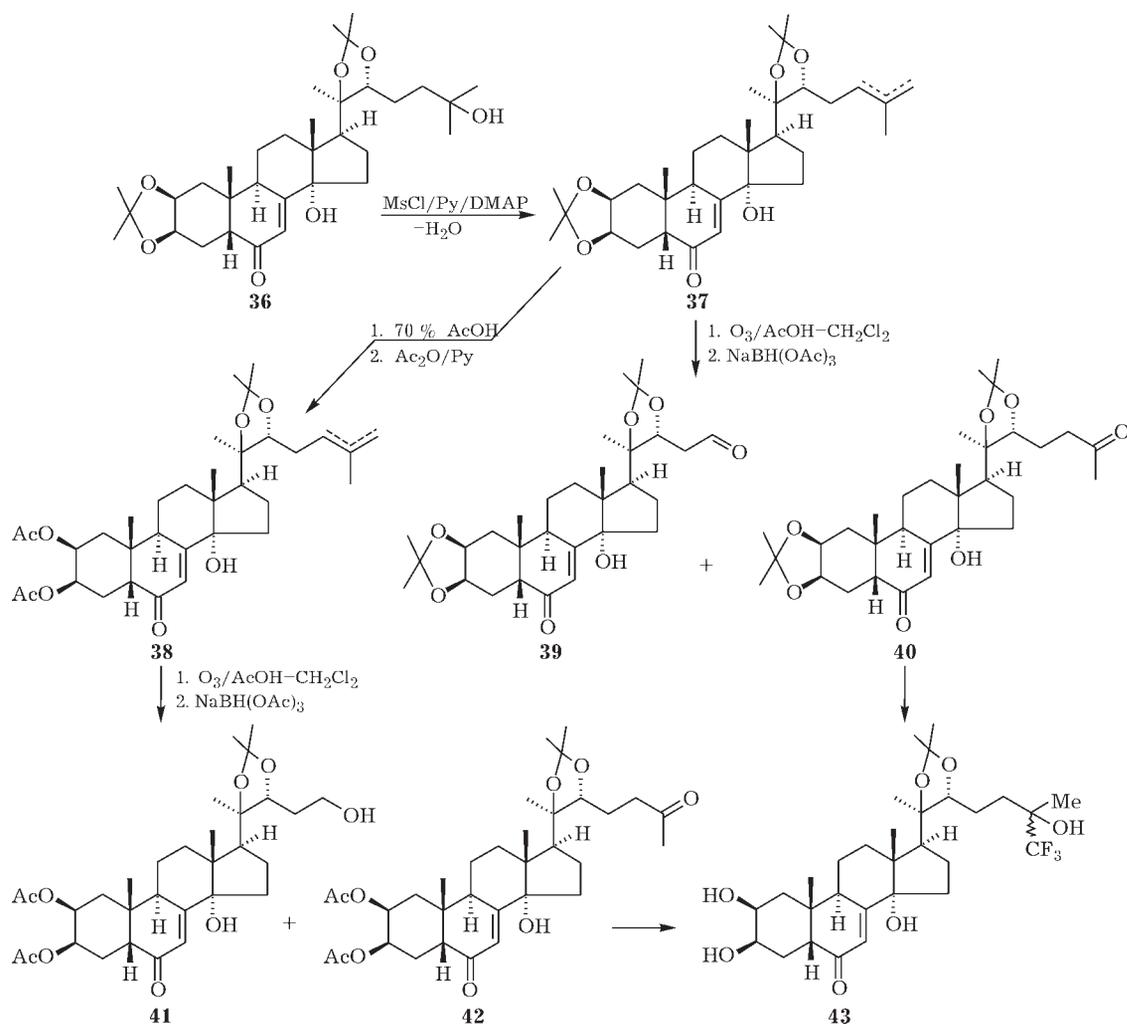
α -tocopherol [33] and its benzoannulated analogue (naphtotocopherol) [36] with an (*R,R*)-configurationally uniform side chain.

During the recent years, a considerable attention is given to the synthesis of water-soluble analogues of vitamin E necessary for realizing the antioxidant functions in hydrophilic media [37, 38]. In order to perform the synthesis of such compound one needs for the presence of chromanes functionalized at the terminal position of a side chain **28**. We have developed the synthesis of these compounds through the ozonolysis of the terminal isopropylidene group in condensation products **27** obtained from the reaction between isoprenoid methylvinylcarbinols **25** and trimethylhydroquinone **26** (Scheme 8) [39, 40].

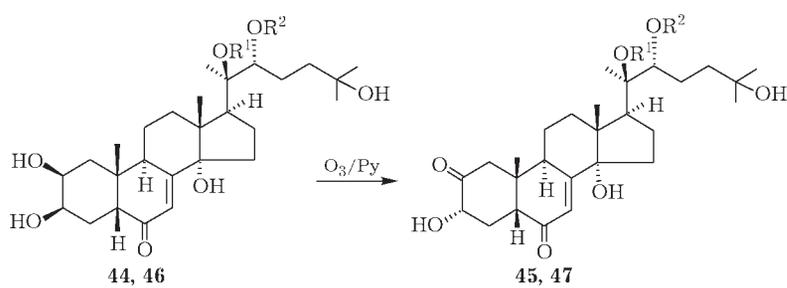
In a similar manner, using the ozonolysis of benzochromanes **30** – the products of carbinols **25** condensation with 2-methyl-1,4-dihydroxynaphthalene acetate **29** – we have obtained the analogues of naphtotocopherol **31** with the functional group in ω position (see Scheme 8) [41]. Aldehydes **28** and **31** have been oxidized to produce corresponding chromane- and benzochromanepropionic acids (**32** and **33**, respectively), and after the conversion of aldehydes **28** and **31** into enolacetates and their ozonolysis we have synthesized substituted acetic acids **34** and **35**, respectively (see Scheme 8) [42].

In the chemistry of ecdysteroids – ecdysis (molting) and metamorphosis hormones of insects – the ozonolysis is used rather seldom [26], which is caused by spatial hindrances for ozone attacking the unique Δ^7 bond conjugated with the 6-keto group. We have proposed a method for the functionalization of a side chain of ecdysteroids based on the ozonolysis of the double bonds in compounds **37** and **38** formed due to the anhydridization of 20-hydroxyecdysone diacetone **36** with respect to the 25-hydroxy group (Scheme 9) [43]. Mixtures of aldehyde **39** and ketone **40** or alcohol **41** and ketone **42** were obtained (at a ratio ~1 : 2) those were separated with the help of a column chromatography. Trifluoromethylation of ketones **40** and **42** resulted in synthesizing of trifluoro substituted analogues of 20-hydroxyecdysone **43** (see Scheme 9) [44].

We have succeeded in realizing the capability of secondary alcohols to be oxidized under the action of ozone with the formation of ketones within the series of ecdysteroids [45]. The ozonization of 20-hydroxyecdysone **44** in pyridine at one stage resulted in the obtaining of 2-dehydro-3-*epi*-20-hydroxyecdysone (Scheme 10), a minor ecdysteroid isolated recently from seeds of *Froelichia floridana* plant species [46] and synthesized by means of six-stage transformations of the same initial compound [47].



Scheme 9.



Scheme 10.

One can see that the ozonization of ecdysteroid **44** results in the selective oxidation of 2-hydroxy group (axial bond C²-H being under attack with the formation of α -hydroxyhydroperoxide undergoing the transformation, according to data from [45], into 2-ketone, at that 3-hydroxy group undergoes epimerization).

The ozonization of 20,22-acetonide of 20-hydroxyecdysone **46** under the same conditions resulted in the obtaining of 20,22-acetonide of 2-dehydro-3-*epi*-20-hydroxyecdysone **47**, whereas 2,3:20,22-diacetonide **36** under the same conditions did not change.

Thus, controlled ozonolysis of alkenes is an efficient and selective method of organic synthesis. It is demonstrated that this method offers new, much more ample potentialities for the application in the chemistry of low-molecular bioregulators.

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