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Insect Exo- and Endohormones: Synthesis and Creation of Preparations for the Regulation of Their Numbers, Behaviour and Vital Functions

G. YU. ISHMURATOV[1], M. P. YAKOVLEVA[1], N. M. ISHMURATOVA[1], V. A. VYDRINA[1], R. R. MUSLUKHOV[1] and G. A. TOLSTIKOV[2]

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

E-mail: insect@anrb.ru

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

Abstract

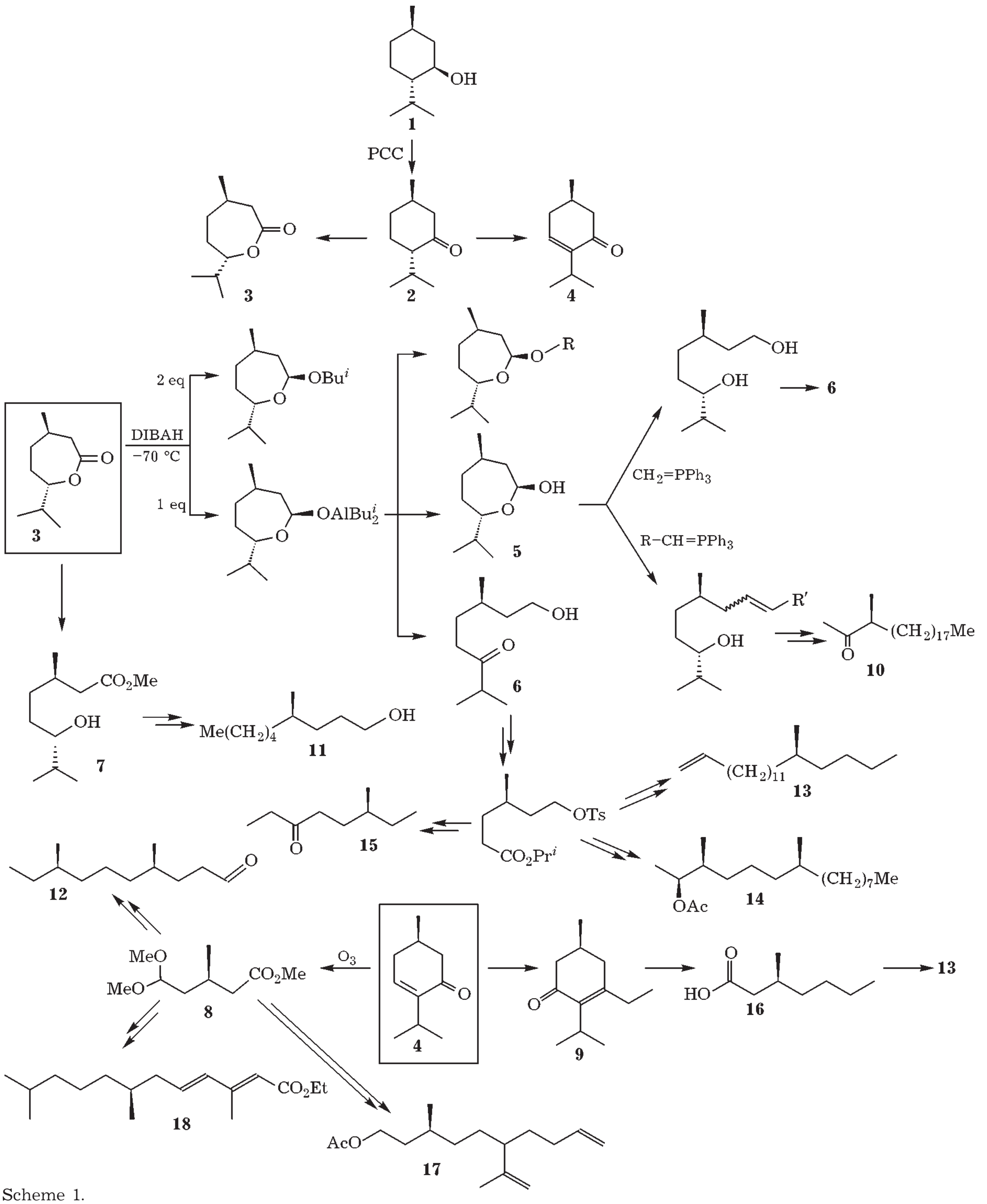
Potentialities were studied with respect to using 4-methylhydropyrane as well as mint and castor oils for the synthesis of low-molecular insect bioregulators and the creation of biologically active preparations for beekeeping basing on synthetically obtained metabolites of the honeybee (*Apis mellifera* L.).

Key words: feromone, juvenoid, l-menthol, ricinoleic acid, 4-methylhydropyrane, 9-oxo and 10-hydroxy-2E-decenic acids, synthesis

For the directed synthesis of insect exo- and endohormones, as an initial raw material we used the materials both of natural origin [castor and mint oils being the sources of optically pure (*R*,*Z*)-(+)-12-hydroxy-9-octadecene (ricinoleic) acid and *l*-menthol, respectively], and of synthetic origin (4-methyltetrahydropyrane, an easily accessible hydrogenation product of so called dihydropyrane fraction representing wastes resulting from isoprene industrial production).

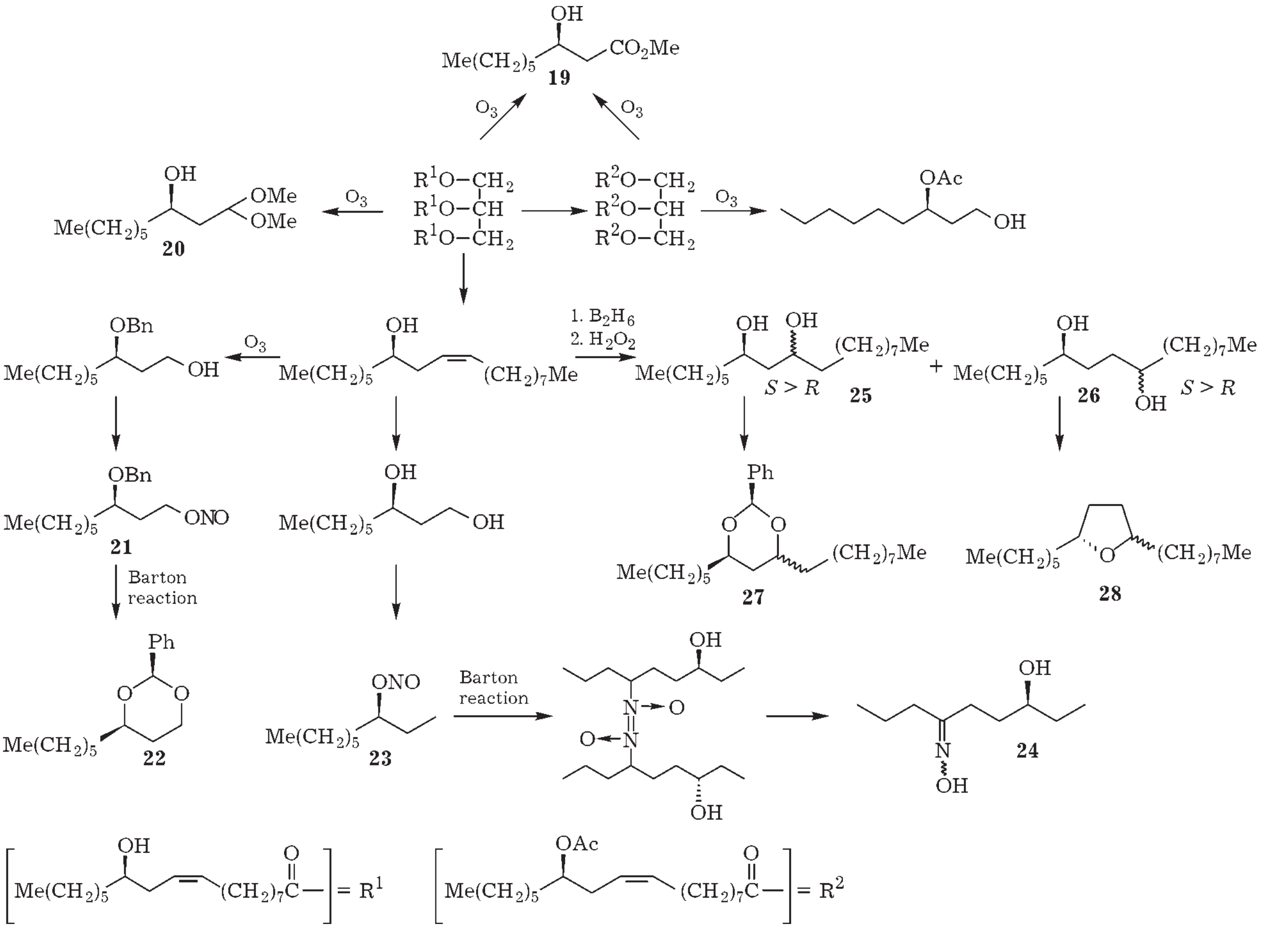
Up till now *l*-menthol **1** has not obtained due application in the chemistry of insect low-molecular bioregulators and other biologically active substances. The use of this substance in the synthesis of chiral building blocks is unreasonably limited, first of all, due to an inertness of the cyclohexane ring. We have proposed methods for activating the cycle by means of transformation through intermediate (−)-menthone **2** to produce (−)-mentholactone **3** or (*R*)-4-menthenone **4** those basing on the reactions of low-temperature hydride reduction and ozonolysis, respectively, have been converted into optically pure block synthons **5–9** and then into pheromones with the naturally occurring configuration inherent in some insects: croton-bug cockroach *Blattella germanica* **10**, mealworms belonging to species *Tenebrio molitor* **11** and genuses *Tribolium* **12**, peach leaf miner *Lyonetia clerckella* **13**, sawflies belonging to genuses *Diprion* and *Neodiprion* **14**, ants of genus *Crematogaster* **15**, scarab beetle *Coleoptera scarabaeidae* **16** and California red scale *Aonidiella aurantii* **17**, as well as into juvenoid (*S*)-(+)-hydroprene **18** (Scheme 1) [1, 2].

In order to extend the synthetic potential of ricinoleic acid derivatives we performed oxidation transformations (ozonolysis, remote functionalization of the chemically stable alkyl part (C-13–C-18) of the molecule under the conditions the Barton reaction and hydroboration–oxidation process) [3–5]. In the course of these studies a novel approach has been developed to the synthesis of methyl (*R*)-3-hydroxynonanoate **19** and acetal of (*R*)-3-hydroxynonanal **20**, the precursors of a microcomponent of human blood plasma, which approach is based on ozonolytic decomposition of ricinoleic acid derivatives with the use of hydroxylamine hydrochloride at the stage of the reduction of peroxide products of ozonolysis. It has been established as well that the photolysis of (3*R*)-benzyloxy-1-nonylnitrite **21** proceeds in a non-traditional manner as 1,6-ab-

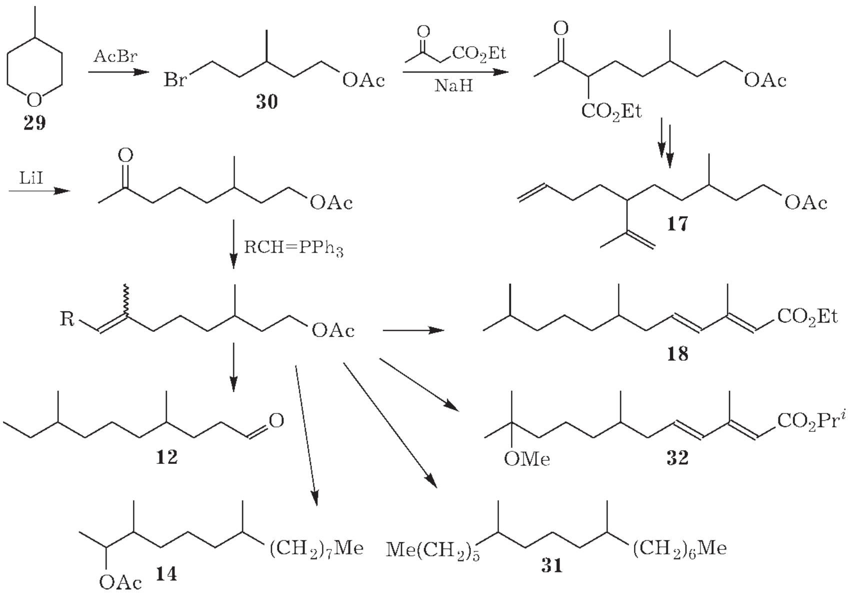


Scheme 1.

straction with the formation of (2*S*)-phenyl-(4*R*)-hexyl-1,3-dioxane **22**; (3*S*)-nonylnitrite **23** under the same conditions is converted into 6-nitroso-(3*S*)-nonanol **24** with a modified akyl part of the initial molecule. It is demonstrated that the optically active centre of ricinoleic acid derivatives insignificantly influences the regioselectivity in the course of the hydroboration–oxidation reaction, which is indicated by the prevalence (6–10 %) of 1,3-diol **25** as compared to its 1,4-isomer **26**; at the same time the optically active center induces the formation of new asymmetric centres mainly with (*S*)-configuration, which has been proved by the cyclization



Scheme 2.



Scheme 3.

of 1,3-glycol **24** (*de* 32–50 %) to produce corresponding stereoisomeric 1,3-dioxane **27**, and the cyclization of 1,4-diol **26** (*de* 22–40 %) to yield 2,5-dialkylsubstituted tetrahydrofuran **28** (Scheme 2).

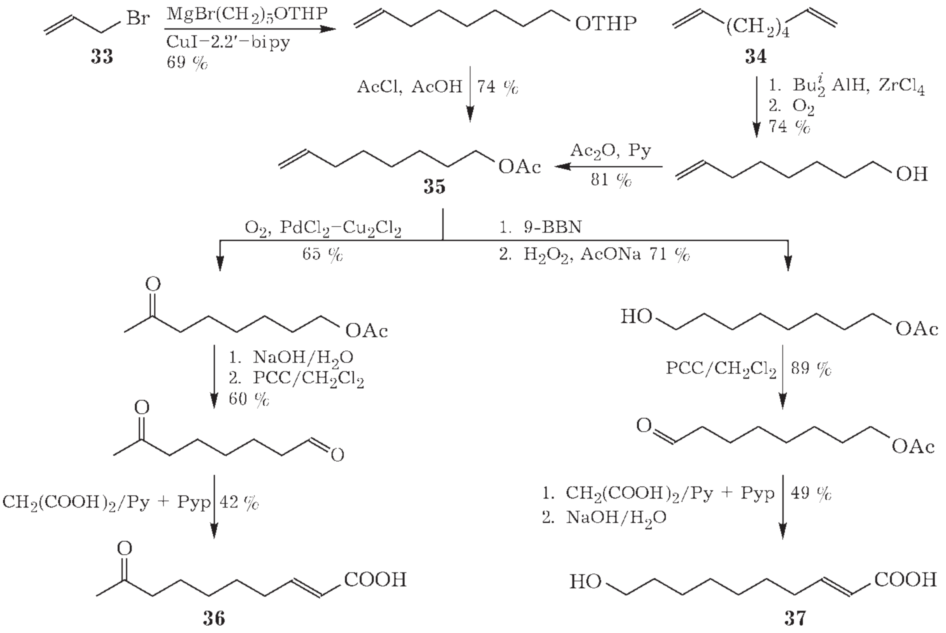
An universal approach has been developed to the synthesis of racemic analogues of aforementioned methyl-branched insect pheromones (**12**, **14**, **17**), yellow-fever mosquito *Aedes aegypti* **31** as well as juvenoids hydroprene **18** and methoprene **32**, basing on the alkylation of acetoacetic ester with 1-acetoxy-5-bromo-3-methylpentane **30** being a product of acidic decyclization of 4-methyltetrahydropyrane **29** (Scheme 3) [6].

Using the theory of pheromone communication in insects we have formulated and developed the prospective scientific direction aimed at the creation of preparations for beekeeping and veterinary medicine based on synthetically obtained metabolites of honybees *Apis mellifera* L. (biologically active components of “queen substance”, “royal jelly” and the Nasonov gland).

In order to solve these problems we have proposed two approaches to the synthesis [7] of biologically active 9-oxo- and 10-hydroxy-2*E*-decenic acids (**36** and **37**, respectively), starting from allylchloride **33** and 1,7-octadiene **34** with the use of chemo- and regioselective transformations of a common intermediate building block such as 7-octene-1-yl acetate **35** (Scheme 4).

For the multipurpose honeybee pheromone such as 2*E*-unsaturated ketoacid **36** we have revealed new outstanding pharmacological properties unknown earlier: antibacterial ones (with respect to the infections caused by Aurococcus, Bacillus proteus, Escherichia coli and blue pus bacillus), as well as anti-inflammatory ones (in the models of formalin, protein and lidocaine inflammation). This pheromone also promotes the healing of flap wounds and thermal burns and plays the role of an immunomodulator, which confirms the thesis by the classics of beekeeping: “Bad queen means bad hive”. (In our opinion, besides numerous already well-known functions, a “queen of beehive” carries out also a medical function which is directly correlated with the amount of 9-oxo-2*E*-decenic acid **36** and, hence, with the quality of a queen.)

The pheromone compositions created using the theories of insect pheromone communication on the basis of synthetic components of “royal jelly“, “queen substance” and the Nasonov gland such as “Apimil” (for the attraction, trapping of hives as well as to prevent hives from meeting in bee-gardens during the swarming), “Mellan” (in order to suppress the aggression of bees while working with them), “Apisil” (for the stimulation of the growth and development of beer hives during the summer



Scheme 4.

and autumn seasons and for the reduction of hiving tendency), “Candisil” (for the stimulation of growth and development of beer families during the early-spring period of year), “Biosil” (to stimulate and enhance taking the maggots for queen nurture in the case of queens withdrawal and the manufacture of royal jelly with a partial or complete orphaning of bee hives) as well as “Opylil” (for correcting the flying activity of honeybees) are recommended for wide field testing over the territory of the Russian Federation.

The application of modern methods for the regulation of vital functions and behaviour of honeybees with the help of pheromone preparations would promote the transformation of Russian beekeeping into a highly profitable branch of agriculture [8].

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