SYNTHESIS OF MACROLIDE PHEROMONES

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This review considers pathways for the synthesis of macrocyclic lactones (macrolides) identified as components of pheromones of insects of the order Coleoptera (Cucujidae), genera Cryptolestes and Oryzaephilus — granary pests.

Interest in the synthesis of macrolides is due above all to the fact that highly active bioregulators are found among the compounds of this class [1, 2]. In the mid-eighties, macrolide components were identified in the secretions of insects of the order Coleoptera (Cucujidae), genera Cryptolestes and Oryzaephilus, which are pests of grain stores [3-7]. Somewhat later [8], a macrolide component was found in the pheromone of the Caribbean fruit fly Anastrepa suspensa — a pest of citrus fruits. At the present time eight macrolide pheromones have been identified. Of them, two (1, 2) have an isoprenoid structure with two double bonds in the ring, while three (3-5) are monoenic, and three (6-8) are dienic. In addition, the saturated macrolide (9) — dihydrorecifeiolide has been detected in the extraction mixture obtained during the isolation of the pheromone of the rusty grain beetle Cryptolestes ferrugineus [3].

As a rule, the strategy of the synthesis of macrolide pheromones is based on the preparation of an acyclic precursor — a hydroxycarboxylic acid — followed by its cyclization. Recently, a method of enzymatic macrolactonization has been used in the synthesis of four macrolide pheromones [8].

SYNTHESIS OF ISOPRENOID MACROLIDES

4,8-Dimethyldeca-4E,8E-dienolide (1) (ferrulactone I) has been identified as the main component of the aggregation pheromone of the rusty grain beetle Cryptolestes ferrugineus [3]. The maximum attractive activity is possessed by a mixture of ferrulactone I (1) and ferrulactone II (4) in a ratio of 9:1 [9].

The majority of syntheses of the eleven-membered macrolide (1) are based on the lactonization of 10-hydroxy-4,8-dimethyldeca-4E,8E-dienoic acid (10) [8, 10-13], for which a number of methods of synthesis have been described [14, 15]:

The isoprenoid structure of ferrulactone I (1) determined the choice of geraniol (11) [10-12, 16] and farnesol (12) [13] as the initial compounds for its synthesis. When geraniol is used, the carbon chain must be extended from its tail by two carbon atoms, while farnesol must be shortened by three carbon atoms.

In the first synthesis of macrolide (1) [10], the key stage was the alkylation of the ω-bromo derivative (13) of geraniol with the lithium salt of 2,4,4-trimethyl-2-oxazoline (14), with the subsequent hydrolysis of the oxazoline (15). The overall yield was 4.4%, calculated on the initial (11):

In the following syntheses, the same authors [10] made use of the alkylation of geraniol bromoacetate (16) with the aid of sodiomalonic ester, leading in high yield to compound (17), the decarboxylation of which gave the acetoxyester (18). In this case, the overall yield of macrolide (1) amounted to 15.5%, calculated on the geraniol (11):

The use of a palladium catalyst in the condensation of chloride (19) with sodiomalonic ester enabled the yield of compound (17) to be raised to 92% [14]. The overall yield of hydroxy acid (10) amounted to 42%, calculated on the geraniol (11):