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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Modified Ozonolytic Synthesis of 4*Z*-Nonen-1-ol, an Intermediate for the Synthesis of Sex Pheromones of Cotton Bollworm and Cabbage Moth, from the Cyclic Butadiene–Isoprene Codimer

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Abstract—An improved procedure for preparing 4*Z*-nonen-1-ol, a key intermediate in the synthesis of sex pheromones of cabbage moth and cotton bollworm, from the cyclic butadiene–isoprene dimer (1-methyl-1*Z*,5*Z*-cyclooctadiene) was developed. In this procedure, the peroxide product of regioselective partial ozonolysis (0.9 equiv of O_3) of the codimer across the trisubstituted double bond is converted in one step to 9-hydroxy-5*Z*-nonen-2-one with $NaBH(OAc)_3$, the reagent that does not affect the keto groups present in the structure or formed in the process.

Keywords: ozonolysis, 1-methyl-1*Z*,5*Z*-cyclooctadiene, 9-hydroxy-5*Z*-nonen-2-one, 4*Z*-nonen-1-ol, sodium triacetoxyborohydride

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The more than half-century history of the "pesticide era," in which the pest control was based on searching for more effective and environmentally acceptable insecticides, i.e., compounds that kill insects, revealed well-known drawbacks of pesticides: toxicity, low specificity to the required species, and rapid development of mechanisms for neutralization of these xenobiotics. Insecticides of new generation, insect pheromones, which act by a different mechanism and are environmentally safe, are free of these drawbacks. Pheromones, which are produced and released into the environment by the insects themselves, are biologically active substances affecting the physiological state and behavior of other individuals of the same species. Knowing the quantitative ratio and chemical structure of the pheromone components, one can synthesize them and formulate pheromone compositions. The use of these compositions allows controlling the behavior of insects: directing them to adhesive traps, misorienting them in search for a partner, taking them off from the plants populated by them, etc. Therefore, pheromone agents occupy an important place in the integrated plant protection, and the development of optimum schemes for preparing the pheromone components is a topical problem [1–4], because these components are usually produced by insects in extremely small (nanogram) amounts, and the only real procedure of their preparation for practice is directional chemical synthesis.

Cotton bollworm (*Heliothis armigera*) and cabbage moth (*Mamestra brassicae*), whose larvae feed on many plants, including cultivated plants, are dangerous polytrophic pests of agricultural crops. The main components of their sex pheromones, derivatives of 11*Z*-hexadecen-1-ol (**1**) [11*Z*-hexadecenal (**3**) and 11*Z*-hexadecen-1-yl acetate (**2**)], were prepared previously by the "acetylene" method via the corresponding alkynes, by Wittig olefination of carbonyl compounds, and by modification of the carbon skeleton in *Z*-unsaturated compounds [5, 6].

This study was aimed at developing a modified ozonolytic procedure for preparing 4*Z*-nonen-1-ol (**4**), an intermediate for the synthesis of pheromones **2** and **3**, from the cyclic butadiene–isoprene codimer (**5**).

EXPERIMENTAL

The IR spectra were recorded with an IR Prestige-21 device (Fourier Transform Spectrophotometer, Shimadzu) from thin layers, and the NMR spectra, with a Bruker AvanceIII 500 spectrometer [operating frequencies 500.13 (^{1}H) and 125.76 MHz (^{13}C)] from solutions in $CDCl_3$, with tetramethylsilane as an internal reference. Gas–liquid chromatography was performed with Chrom-5 [column length 1.2 m, stationary phase 5% SE-30 on Chromaton N-AW-DMCS (0.16–0.20 mm), working temperature 50–300°C] and Chrom-41 (column length 2.4 m, stationary phase PEG-6000, working temperature 50–200°C) devices using helium as a carrier gas. Thin-layer chromatography was performed on SiO_2 of Sorbfil grade (Russia). Column chromatography was performed on SiO_2 (70–230 mesh, Lancaster, the United Kingdom). The results of elemental analysis of all the compounds agreed with the calculated data. The ozonizer capacity was 40 mmol of O_3 per hour.

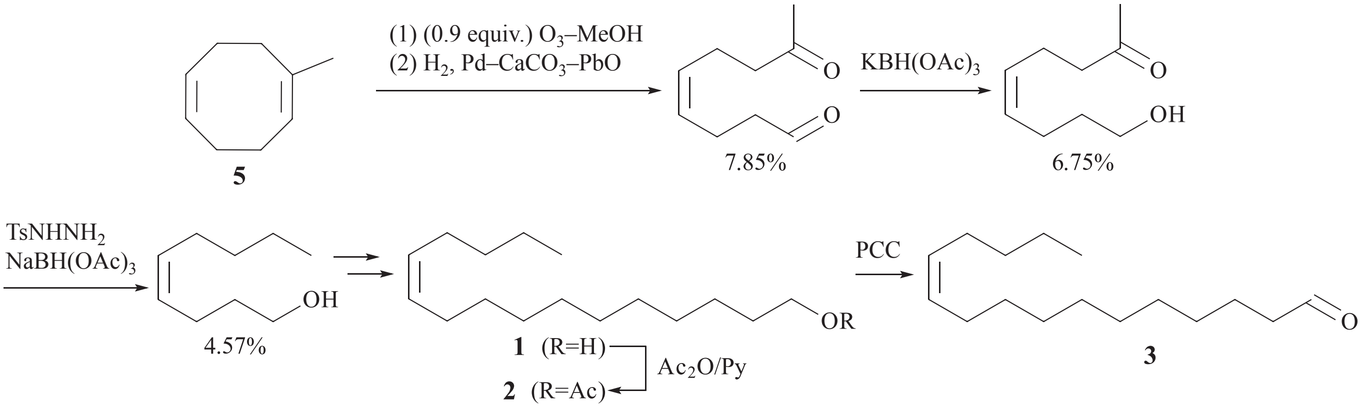
9-Hydroxy-5Z-nonen-2-one (6). An ozone–oxygen mixture was bubbled at 5°C through a solution of 1.95 g (16.0 mmol) of cyclodiene **5** in 16 mL of distilled cyclohexane, containing 1.85 mL (32.0 mmol) of glacial acetic acid, until 14.4 mmol of ozone was taken up. Then, the reaction mixture was purged with argon, the solvent was separated from the precipitated peroxide product by decantation, and the product was dissolved in 45 mL of methylene chloride and added with stirring at 10°C to a preliminarily prepared $NaBH(OAc)_3$ suspension [prepared by adding a solution of 11.9 g (198.0 mmol) of glacial AcOH in 20 mL of CH_2Cl_2 to a suspension of 2.50 g (66.0 mmol) of $NaBH_4$ in 100 mL of CH_2Cl_2 and stirring for 2 h]. Then, the reaction mixture was allowed to warm to room temperature, stirred for 3 h, and cooled to 10°C, and a solution of 4.5 g of NaOH in 100 mL of water was added. The organic layer was separated, washed in succession with a saturated NH_4Cl solution and water, dried over Na_2SO_4, and evaporated. 1.92 g (85%) of keto alcohol **6** of 96% chemical purity (capillary GLC data) was obtained. The IR and NMR spectra of the product virtually coincide with those described in [7].

4Z-Nonen-1-ol (4). 80% hydrazine hydrate (1.88 g, 30.0 mmol) was added dropwise at 15°C to 1.56 g (10 mmol) of 9-hydroxy-5*Z*-nonen-2-one (**6**) dissolved in 10 mL of diethylene glycol. The mixture was stirred for 3 h and allowed to stand for 16 h at room temperature. Then, 2.8 g (50.0 mmol) of KOH was added, the mixture was refluxed for 2 h, water and excess hydrazine hydrate were distilled off by heating the mixture to 195°C, and the mixture was heated at 195°C for an additional 4 h, cooled to room temperature, diluted with 10 mL of water, and extracted with diethyl ether (4 × 50 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed (SiO_2, hexane–Et_2O, 3 : 1) to obtain 0.98 g (68%) of alkenol **4**. The IR and NMR spectra of the product were identical to those described in [8].

RESULTS AND DISCUSSION

Success in catalysis of the oligomerization of the simplest 1,3-dienes and alkenes by metal complexes makes various unsaturated compounds of regular structure, in particular, cyclic di- and trienes, synthetically accessible. In turn, the subsequent chemo- and regioselective cleavage of one of the multiple bonds in such cyclopolyenes opens efficient synthetic routes to acyclic α,ω-bifunctional unsaturated block intermediates capable of further chemoselective transformations in directional synthesis of biologically active compounds, including low-molecular-mass insect bioregulators, containing *Z*- or *E*-alkene fragments [9].

Efficient synthesis of a series of insect pheromones, including pheromones **2** and **3**, based on selective partial ozonolysis of the cyclic isoprene–butadiene codimer, 1-methyl-1*Z*,5*Z*-cyclooctadiene (**5**) [10], was reported previously [7]. Partial ozonolysis with 0.9 equiv of ozone occurs with 90% selectivity across the trisubstituted double bond at 5°C in cyclohexane in the presence of 4 equiv of methanol. The subsequent reduction with hydrogen over Lindlar catalyst yields keto aldehyde **7**. Treatment of the latter with potassium triacetoxyborohydride yields unsaturated hydroxy ketone 6 whose conversion to the corresponding tosylhydrazone and subsequent reaction with sodium triacetoxyborohydride yields 4*Z*-nonen-1-ol (**4**). Its overall yield based on substrate **5** is 36%. Homologization of the key alkenol **4** to 11*Z*-hexadecen-1-ol (**1**) and then to the desired pheromones **2** and **3** was performed by the Li_2CuCl_4-catalyzed cross coupling of 4*Z*-nonen-1-ol tosylate with the Grignard reagent derived from 7-bromo-1-(1-ethoxy)ethoxyheptane, followed by acid hydrolysis and subsequent chemoselective oxidation with pyridinium chlorochromate or acetylation under standard conditions:



In this study, we optimized the ozonolytic synthesis of keto alcohol **6**, the base intermediate for preparing pheromones **2** and **3**, from the same substrate **5**. To this end, we performed its partial ozonolysis with 0.9 equiv of O_3 in cyclohexane in the presence of 2 equiv of glacial acetic acid. As a reducing agent we used NaBH$(OAc)_3$, which was successfully used previously [11, 12] as a chemoselective hydride agent for peroxide ozonolysis products, leaving intact the keto groups present in the structure or formed in the process. This allowed us to eliminate one of the steps (synthesis of keto aldehyde **7**), reduce the number of reagents, and increase the yield of unsaturated keto alcohol **6**. The Huang–Minlon reduction of **6** in diethylene glycol via the corresponding hydrazone gave the key compound, 4*Z*-nonen-1-ol (**4**), in an overall yield of 57%, which was more than 20% higher than the yield in the previously reported three-step synthesis:

$$\mathbf{5}\ \xrightarrow[\text{(2) NaBH(OAc)}_3]{\text{(1) (0.9 equiv.)O}_3\text{, }c\text{-C}_6\text{H}_{12}\text{, AcOH}}\ 6.85\%\ \xrightarrow[\text{(2) KOH, }\Delta]{\text{(1) NH}_2\text{NH}_2\cdot\text{H}_2\text{O, DEG}}\ 4.68\%.$$

CONCLUSIONS

We have modified the ozonolytic synthesis of 4*Z*-nonen-1-ol, a key intermediate in the synthesis of the major component of sex pheromones of cotton bollworm and cabbage moth. Our procedure is based on the use of sodium triacetoxyborohydride, which chemoselectively reacts with the peroxide ozonolysis products and aldehydes without affecting keto groups. This allowed us to eliminate one of the steps and increase the overall yield by more than 20%.

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