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The Synthesis of 1-Hydroxy-5-Nonanone: A Volatile Substance Released by *Bactrocera cacuminatus*[+]

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Descreve-se a síntese da 1-hidroxi-5-nonanona com utilização da ciclopentanona como material de partida, em quatro etapas e atingindo 33% de rendimento global.

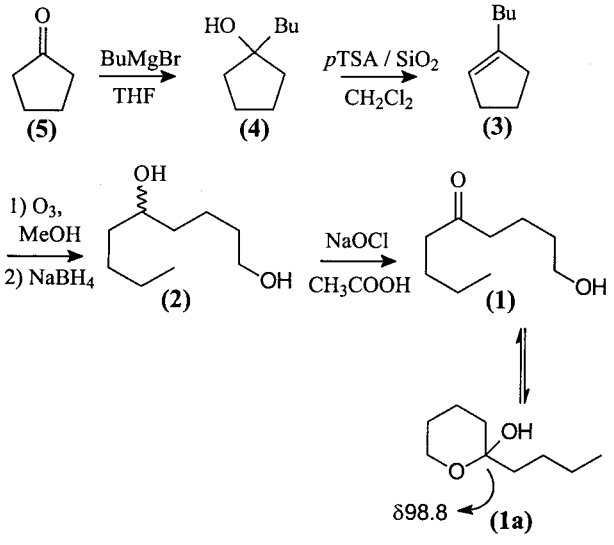
The expeditious synthesis of 1-hydroxy-5-nonanone is described, starting from cyclopentanone, in four steps and with a good yield.

Keywords: *1-hydroxy-5-nonanone,* Bactrocera cacuminatus, *selective oxidation*

Introduction

Bactrocera cacuminatus (Héring) along distributed in the coastal regions of eastern Australia. This medium-sized species has been regarded as a minor tomato and capsicum pest in Queensland[1].

In this work, we describe the synthesis of 1-hydroxy-5-nonanone **(1)** (Scheme 1), which was identified and synthesized in 1991 by Kitching and co-workers[1] as a minor component of the rectal glandular extract and volatile emission of the male *Bactrocera cacuminatus*[2].



Scheme 1. The synthesis of 1-hydroxy-5-nonanone **(1)**.

Results and Discussion

The alcohol **(4)** was obtained through a Grignard reaction of BuMgBr with cyclopentanone **(5)** in a 65% yield[3]. To dehydrate the tertiary alcohol we introduced a modification in the method previously published by D'Onofrio and Scettri[4] using *p*-toluenesulfonic acid adsorbed onto silica gel. The alcohol was percolated through a short chromatographic column packed with *p*-TSA/silica gel, and eluted with CH_2Cl_2, affording the endocyclic olefin **(3)**[5] in a 77% yield. Ozonolysis[6] of this olefin in methanol at -60 °C, followed by reduction with $NaBH_4$, afforded the intermediate diol **(2)** in a 90% yield.

The hydroxy-ketone **(1)** was obtained by selective oxidation of the secondary hydroxyl group of the diol **(2)**, with NaOCl in acetic acid[7,8] in a 75% yield. It is important to note that the reaction work up has to be done in a controlled manner, otherwise the cyclized hemiacetal **(1a)** can become the major, if not the only product. To prevent this, it is very important to wash the organic layer with aqueous $NaHCO_3$. The presence of the cyclic hemiacetal **(1a)** can be easily characterized by its ^{13}C-NMR signal[1] at δ 98.8.

Experimental

The IR spectra refer to films and were measured on a Bomem M-102 spectrometer. The ^{1}H-NMR spectra were

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recorded with TMS as an internal standard at 400 MHz on a Bruker ARX-400 spectrometer. The ^{13}C-NMR spectra were recorded with TMS as an internal standard at 100 MHz on a Bruker ARX-400 spectrometer. Samples were analyzed by GC on a HP-Carbowax 20 M column (0.11 μm film, 25 m long, 0.20 mm ID) using a HP-5890 series II gas chromatograph with nitrogen as the carrier (1mL/min), and a temperature program from 70 °C for 1 min to 200 °C at 7 °C/min with a 2 min final hold . Column chromatography was carried out on columns packed with Merck Kieselgel 60, Art.-Nr. 7734.

1-Butyl Cyclopentanol (4): A Grignard reagent was prepared from butyl bromide (9.65 g; 75.5 mmol; 7.55 mL) and Mg (2.20 g; 90.0 mmol) in dry THF (115 mL). Cyclopentanone **(5)** (3.15 g; 37.5 mmol; 3.30 mL) was added by drops (2.0 h) to the organomagnesium reagent at room temperature and stirred for 3.0 h. A solution of saturated NH_4Cl (30.0 mL) was added and the reaction mixture was extracted with ether, dried (Na_2SO_4) and concentrated. The residue was fractionated (30 °C; 1.5 mmHg) and the alcohol **(4)** was obtained in a 65% yield (3.50 g). [GC, *R*t = 3.40 min; IR ($\nu_{max.}$ film cm^{-1}): 3382, 2946, 2866, 1459, 1380; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.85 (t, J = 7.20 Hz, 3H); 1.26-1.33 (m, 4H); 1.48-1.58 (m, 9H); 1.72-1.75 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.01; 23.21; 23.72; 26.81; 39.51; 39.67; 41.14; 53.32; 82.45].

Preparation of the p-toluene sulfonic acid / silica gel reagent[4]: silica gel (100.0 g) was added to a solution of *p*-toluene sulfonic acid (3.0 g) in 15.0 mL of acetone. The resulting slurry was homogenized in a rotary evaporator without vacuum for 1 h. Then, vacuum was applied and the solvent was evaporated under reduced pressure to give a free-flowing solid, which was kept under vacuum (1.5 mmHg) at room temperature for 7 h.

1-Butyl cyclopentene (3): a chromatographic column was packed with a slurry of *p*-TSA/SiO_2 reagent in CH_2Cl_2 (the reagent pad measured 2.5 cm x 30.0 cm), and the alcohol **(4)** (1.5 g; 10.0 mmol) was percolated through the column under pressure using CH_2Cl_2 as the eluting solvent. The product **(3)** was collected in a round-bottomed flask, and the CH_2Cl_2 was carefully evaporated. 1-Butyl cyclopentene was obtained in a 77% yield (1.0 g; 8.0 mmol), and was utilized in the next step without further purification.

1,5 - Nonane diol (2): O_3 in oxygen was bubbled into a cooled solution of **(3)** (1.0 g; 8.0 mmol) in dry methanol (100 mL) at -60 °C until saturation (blue color). This solution was purged with a stream of oxygen to remove the excess ozone. Then, $NaBH_4$ (2.00 g; 53.8 mmol) was added by portions, over a 1 h period, at 0 °C under magnetic stirring, and the reaction was left at that temperature for 4 h. The solvent was evaporated under reduced pressure and the residue was treated with a saturated NH_4Cl solution and extracted with ether. The usual work-up gave a crude product which was purified by flash cromatography (hexane:ethyl acetate / 1:1) to afford the diol **(2)** in a 91% yield (1.20 g). [GC, *R*t = 13.72 min; IR ($\nu_{max.}$ film cm^{-1}): 3318; 2935; 2865; 1453; 1036; ^{1}H-NMR (400 MHz-$CDCl_3$) δ: 0.84 (t, J = 6.80 Hz, 3H); 1.23-1.52 (m, 12H); 2.81 (br. s, 2H); 3.55-3.56 (m, 1H); 3.60 (t, J = 6.00 Hz, 2H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.25; 22.06; 22.96; 28.07; 32.82; 37.20; 37.47; 62.98; 72.14].

1-Hydroxy-5-nonanone (1): the diol **(2)** (0.24 g; 1.50 mmol) was dissolved in 1.5 mL of glacial acetic acid and magnetically stirred. Aqueous 1.86 M NaOCl (1.65 mL; 1.84 equiv.) was added by drops at room temperature for 15 min, which initiated a rapid exothermic reaction. Stirring was continued for one hour at room temperature and then 1.5 mL of isopropanol was added to quench any remaining oxidant, followed by 30 mL of water. The solution was extracted 3 times with CH_2Cl_2, washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. The oil obtained was purified by column chromatography (hexane:ethyl-acetate / 3:1) to afford the hydroxy-ketone **(1)** in a 75% yield (0.17 g). [GC, *R*t = 11.62 min; IR ($\nu_{max.}$ film cm^{-1}): 3420; 2942; 2871; 1711; 1458; 1051; ^{1}H-NMR (400 MHz-$CDCl_3$) δ: 0.83 (t, J = 7.2 Hz, 3H); 1.17-1.33 (m, 2H); 1.44-1.52 (m, 4H); 1.54-1.63 (m, 2H); 2.26 (br. s, 1H); 2.34 (t, J = 7.6 Hz, 2H); 2.39 (t, J = 7.2 Hz, 2H); 3.55 (t, J = 6.4 Hz, 2H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.81; 19.84; 22.36; 26.01; 32.18; 42.30; 42.55; 62.23; 211.64]. The spectroscopy data are in accordance with the literature[1].

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