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A FACILE SYNTHESIS OF THE SEX PHEROMONE OF THE CABBAGE LOOPER *Trichoplusia ni*

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The sex pheromone of the cabbage looper Trichoplusia ni *Hubner, (Z)-7-dodecen-1-yl acetate, was synthesized via a bimolecular nucleophilic substitution reaction between the Grignard reagent of the protected bromohydrin with (Z)-2-hepten-1-yl acetate in the presence of CuI catalyst as a key step. An efficient synthetic method of preparation of the pheromone was achieved from (Z)-2-butene-1,4-diol in four steps with an overall yield of 22.1%.*

Keywords: cabbage looper, Grignard coupling, sex pheromone, *Trichoplusia ni* Hubner.

The cabbage looper *Trichoplusia ni* Hubner is a widely distributed polyphagous insect in North America, Africa, Asia, and parts of Europe. In Vietnam, this pest was found on broccoli, cabbage, tomato, beet, peas, and many weed plants in the Mekong Delta region [1]. The sex pheromone of *Trichoplusia ni* [2], (*Z*)-7-dodecen-1-yl acetate (**1**), was first isolated and identified in 1966. Then Green et al. [3] confirmed its attractiveness to male cabbage loopers in field tests. The observed inhibitory action of the precursor of the pheromone, (*Z*)-7-dodecen-1-ol (**2**), due to its pheromonal activity was reported by Tumlinson′s group [4].

With the aid of the pheromone, effective and cost-efficient control of the insect population can be achieved, hence the task of synthesizing (*Z*)-7-dodecen-1-yl acetate. The pheromone was first synthesized by Berger [2] and improved by Green [3]. Recently, (*Z*)-7-dodecen-1-yl acetate was prepared based on co-metathesis of cycloocta-1,5-diene and ethylene [5–7]. The stereoselective Wittig reaction between 7-hydroxyheptanal and alkylphosphonium salt was employed as a key step in the synthesis of (*Z*)-7-alken-1-ol [8, 9]. Oxidation of boronated esters [10, 11] by treatment of *trans*-1-alkenylborepanes with iodine in the presence of a base has been explored to afford (*Z*)-7-alken-1-ol. Fiandanese et al. [12] have used (*Z*)-1-bromo-2-phenylthioethene as a reagent containing a double bond, via two cross-coupling reactions with Grignard reagents in the presence of two catalysts, Pd (II) and Ni (II) complex. The stereoselective reduction of an acetylenic compound as a classical method has been employed in the synthesis of the pheromone of the cabbage looper [13–16]. However, the drawback of the above approaches is either obtaining a mixture of *E* and *Z* isomer or a difficultly accessible metathesis.

A low-cost method of synthesis is necessary in the practical use of the pheromone to decrease the population of the insect. In addition, we have successfully employed an efficient synthetic procedure to obtain monoene compounds from 2-butyn-1,4-diol using the bimolecular nucleophilic substitution reaction between the Grignard reagent and allyl-bearing variously functional groups [17]. Herein, we describe the development of this method for synthezising the sex pheromone of *Trichoplusia ni* Hubner from commercial (*Z*)-2-butene-1,4-diol using Grignard coupling of the protected bromohydrin in the presence of CuI catalyst as a key step.

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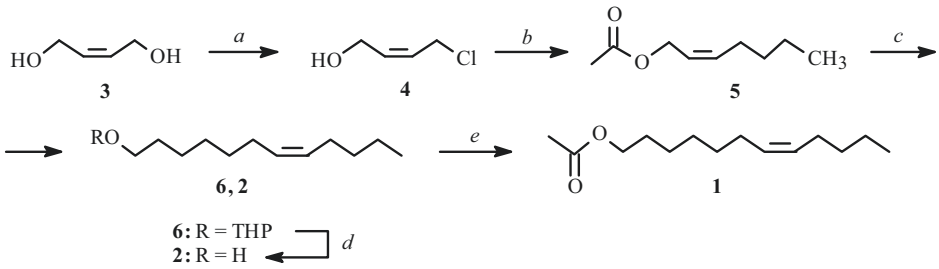

a. $SOCl_2$, reflux, 2h; *b*. 1. *n*-PrMgBr, THF, r.t., 2. Ac_2O, 0°C; *c*. THPO-$(CH_2)_5$-MgBr, CuI, THF, 0°C; *d*. PTSA. MeOH, 50°C; *e*. Ac_2O, Py, 0°C

Scheme 1

The synthetic pathway is shown in Scheme 1. The (*Z*)-2-butene-1,4-diol (**3**) was converted to chlorohydrin **4** by treatment with thionyl chloride in 60.25% yield. After distillation, the intermediate **4** was unstable in light and air, hence it was used for the next step without further purification. Coupling between the Grignard reagent prepared from 1-bromopropane and compound **4** was carried out at ambient temperature in the absence of catalyst. Acetic anhydride was added into the mixture to afford the ester **5** with a yield of over 70% in two steps following the efficient method devised by Iwamoto et al. [19]. Next, the bimolecular nucleophilic substitution reaction of the Grignard reagent (prepared from 2-[(5-bromopentyl)oxy]tetrahydro-2*H*-pyran) with the acetate **5** in the presence of CuI catalyst followed by de-tetrahydropyranylation with PTSA (*p*-toluenesulfonic acid) in methanol at 50°C gave the pheromone inhibitor **2** with a yield of 59.8% in two steps. The residue containing a small amount of by-product was purified by column chromatography using silica gel impregnated with $AgNO_3$ (20%, w/w) as the stationary phase [20, 21]. The pheromone was prepared by esterification of the alcohol **2** in the presence of pyridine as a catalyst with 86.2% yield. All products were characterized by FTIR and NMR spectra, which matched those reported previously [5–7].

EXPERIMENTAL

All manipulations were performed under dry nitrogen atmosphere using Schlenk techniques. The starting (*Z*)-2-butene-1,4-diol was purchased from Merck (Germany). 2-[(5-Bromopentyl)oxy]tetrahydro-2*H*-pyran was prepared as in [18]. The other reagents were purchased from Aldrich. THF was dried with Na/benzophenone and freshly distilled prior to use. The other solvents were purchased from Fluka and used without further purification. Column chromatography was performed with Merck Kieselgel 60. IR spectra were recorded on a Bruker Equinox 55 IR spectrophotometer. ^1H (500 MHz) and ^{13}C (125 MHz) NMR were recorded on a Bruker Avance 500 NMR spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in δ relative to TMS. GC analyses were carried out using an Agilent Technologies 6890N chromatograph (USA). Refractive indices (n_D) were measured with a WAY-2S ABBE refractometer.

(*Z*)-7-Dodecenyl acetate (1) was prepared in the manner reported by Bykov′s group [6] (yield 86.2%, bp 300.1°C, n_D^{28} 1.448). MS *m/z* 226 (M^+). FTIR (KBr, ν_{max}, cm^{-1}): 2926, 2858, 1738 (s, C=O), 1462, 1372, 1346, 1243, 1180, 1096, 1030, 857, 777, 723. ^1H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, t, J = 7.0), 1.23–1.38 (10H, m), 1.64 (2H, m), 2.03 (4H, m), 2.04 (3H, s), 4.06 (2H, t, J = 6.5), 5.36 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 14.10, 21.02, 22.66, 25.86, 27.10, 27.25, 28.89, 29.65, 29.71, 32.00, 64.66, 129.61, 130.13, 171.22.

(*Z*)-7-Dodecen-1-ol (2) was synthesized as follows: the Grignard reagent solution obtained from 2-[(5-bromopentyl)-oxy]tetrahydro-2*H*-pyran (6.82 g, 0.027 mol) and magnesium (1.0 g, 0.041 mol) in anhydrous THF (30 mL) was slowly added dropwise using a syringe to a solution of compound **5** (3.12 g, 0.02 mol) in THF (30 mL) containing a catalytic amount of CuI (0.5 g, 2.5 mmol) at 0°C. After stirring overnight at ambient temperature, the mixture was poured into an aqueous solution of NH_4Cl and extracted with diethyl ether. The organic layer was washed with an aqueous solution of $NaHCO_3$, water, and brine, then dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford 8.2 g of the crude product. A mixture of the crude product, PTSA (300 mg), and methanol (200 mL) was stirred at 50°C for 2 h. The mixture was then concentrated to half volume and poured into the $NaHCO_3$ solution, and the product was extracted with diethyl ether. The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was evaporated. The product was purified on a column of silica gel impregnated with $AgNO_3$ (20%, w/w) using hexane–EtOAc (φ_r = 5:1) to afford (*Z*)-7-dodecen-1-ol (2.20 g, 59.8% yield in two steps, bp 270.1°C, n_D^{28} 1.456). MS *m/z* 184 (M^+). FTIR (KBr, ν_{max}, cm^{-1}): 3339 (br., OH), 2926, 2856, 1462, 1377, 1125, 1125, 1056, 817, 727, 685. ^1H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, t, J = 7.0), 1.20–1.41 (10H, m), 1.59

(2H, m), 2.02 (4H, m), 3.64 (2H, t, J = 6.5), 5.35 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 13.96, 22.34, 25.65, 26.92, 27.12, 29.06, 29.70, 31.96, 32.78, 63.05, 129.70, 130.02.

(*Z*)-4-Chloro-2-buten-1-ol (4) was synthesized as follows: to a three-necked 250 mL round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser and containing (*Z*)-2-butene-1,4-diol (**3**, 26.40 g, 0.30 mol), was slowly added 25.5 mL (41.65 g, 0.35 mol) thionyl chloride dropwise using a syringe. The reaction mixture was refluxed for 2 h. The unreacted $SOCl_2$ was removed under vacuum for 2 h. Then benzene (50 mL) was added, and the solvent was evaporated under reduced pressure on a rotary evaporator to remove sulfur dioxide. The residue was distilled to give 16.15 g of (*Z*)-4-chloro-2-buten-1-ol (60.25% yield), bp 65–75°C (5 mm Hg). The product **4** is unstable in light and air and used without further purification.

(*Z*)-2-Heptenyl acetate (5) was synthesized as follows: the Grignard reagent solution obtained from *n*-propyl bromide (15.87, 0.13 mol) and magnesium (3.35 g, 0.14 mol) in anhydrous THF (100 mL) was slowly added dropwise using a syringe to a solution of (**4**) (9.2 g, 0.086 mol) in THF (30 mL) at 20°C. Then the mixture was stirred at ambient temperature for 6 h (monitored by GC). After cooling to 0–5°C, acetic anhydride (13.80 g, 0.135 mol) in THF (10 mL) was added dropwise, and the mixture was stirred overnight at ambient temperature. The reaction mixture was poured into an aqueous solution of NH_4Cl, and the product was extracted with diethyl ether. The combined organic layers were washed with an aqueous solution of $NaHCO_3$, water, and brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified on a column of silica gel using hexane–EtOAc (φ_r = 10:1) to afford **5** (6.5 g, 71.25%; bp 195.9°C, n_D^{28} 1.436). MS *m/z* 156 (M^+). FTIR (KBr, ν_{max}, cm^{-1}): 3076, 3022, 2958, 2928, 2859, 1742 (s, C=O), 1461, 1373, 1232, 1026, 969, 916, 840, 729, 644, 606. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.92 (3H, t, J = 7.5), 1.26–1.39 (4H, m), 2.06 (3H, s), 2.13 (2H, m), 4.63 (2H, d, J = 7.0), 5.55 (1H, m), 5.67 (1H, m).^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 13.88, 20.99, 22.24, 27.24, 31.59, 60.42, 123.29, 135.46, 171.00.

This work demonstrates a simple and efficient synthetic route for obtaining the sex pheromone of the cabbage looper. The pheromone was synthesized with an overall yield of 22.1% calculated on the starting (*Z*)-2-butene-1,4-diol via four steps. These results contribute to the methodology to further advance the practical use of pheromones as environmentally benign tools for pest control.

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