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Article

A Short and Stereoselective Synthesis of the Sex Pheromone of *Bonagota cranaodes* (Lepidoptera: Tortricidae)

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O acetato de (3E,5Z)-dodecadienila, feromônio sexual da lagarta enroladeira da maçã, *Bonagota cranaodes* (Lepidoptera: Tortricidae), foi estereosseletivamente sintetizado empregando-se uma metodologia envolvendo o acoplamento de Z-alquenil cuprato com 4-iodo-3-butin-1-ol, como etapa chave.

A stereoselective synthesis of (3E,5Z)-dodecadienyl acetate, the sex pheromone of the leafroller moth *Bonagota cranaodes*, was efficiently carried out using a methodology based on the coupling of Z-alkenyl cuprate with 4-iodo-3-butyn-1-ol in the key step.

Keywords: *(3E,5Z)-dodecadienyl acetate, sex pheromone, synthesis*

Introduction

(3E,5Z)-3,5-dodecadienyl acetate was identified by Unelius C.R. *et al.* as the sex pheromone of the leafroller *Bonagota cranaodes* (Lepidoptera: Tortricidae), an economically important insect pest of apples in Southern Brazil. In order to elucidate the pheromone structure this compound was first prepared by a methodology in low stereoselectivity and yield[1].

Recently a concise synthesis was reported by Oh D.Y. *et al.* based on electrophile trimethylchlorostannane-induced rearrangement of lithium 1-octynylborate as the main process[2].

Herein we describe a short and stereoselective synthesis of this pheromone in three steps with 46,8% overall yield.

Experimental

General

Nuclear magnetic ressonance spectra (NMR) were recorded as solutions in $CDCl_3$ on a Brucker AC-400 spectrometer. Chemical shifts are reported in parts per million (δ units) relative to tetramethylsilane as internal standard. Coupling constants are reported in hertz (Hz). The infrared spectra were recorded on a Bomem MB-100 spectrometer. The mass spectra were obtained with a Shimadzu GC-MS-QP5000 instrument equipped with a DB-5 column (30 m x 0.25 mm) and the data are reported as m/z (abundance). Capillary gas chromatography analyses were performed on a Shimadzu GC-14B chromatograph equipped with a DB-WAX column (30 m x 0.25 mm). Flash chromatography was performed on E. Merck silica gel 60 (230-400 mesh). All reactions were monitored by thin layer chromatography (TLC) or capillary GC.

(5Z)-Dodecen-e-yne-1-ol **3**

To a suspention of copper(I) bromide-dimethyl sulphide complex (525 mg, 2.55 mmol) in tetrahydrofuran (10 mL), cooled at -78 °C under nitrogen, was added a solution of hexyl magnesium bromide freshly prepared by addition of hexyl bromide (0.71 mL, 5.1 mmol) to magnesium turnings (0.125 g, 5.1 mmol). Stirring of the resulting reddish solution was maintained for 1 h. Acetylene (132.5 mL, 5.3 mmol), from which acetone was removed by passage through a dry-ice cooled trap, was bubbled into the reaction mixture and then the mixture was brought to -30 °C for 0.5 h, then TMEDA (0.85 mL, 5.5 mmol) was added in solution in THF (10 mL). The temperature was allowed to rise from -30 °C to -15 °C, then cooled to -45 °C, and 1-iodo-4-butynol (0.97 g, 5.1 mmol) was added. The cooling bath was removed and the mixture was allowed to warm to room temperature. A saturated solution of NH_4Cl (5 mL) was added and the aqueous layer was extracted twice with ether. The organic phase was dried over anhydrous magnesium sulphate and concentrated *in vacuo*. Flash chromatography of the residue on silica gel using hexane: ethyl acetate (5:1 ratio) afforded 0.477 g (52%) of compound **3**.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.87 (dt, J = 7.38, 10.73 Hz, 1H), 5.31 (bd, J = 10.73 Hz, 1H), 3.75 (t, J = 6.26 Hz, 2H), 2.63 (dt, J = 2.14, 6.26 Hz, 2H), 2.35-2.25 (m, 2H), 1.50-1.20 (m, 9H), 0.80 (t, J = 6.9 Hz, 3H); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 143.70, 108.76, 90.21, 79.42, 61.27, 31.68, 30.17, 28.80, 23.99, 22.59, 14.07; **IR** (film) ν 3414, 2959, 2928, 2852, 2220, 1664, 1453, 1047, 776; **MS** (70 eV): m/z (%) = 180 (M^+), 123, 96, 91, 77, 66, 41 (100).

(3E,5Z)-3,5-Dodecadienyl acetate **4**

A solution of compound **3** (0.06 g, 0.33 mmol) in diglyme (0.7 mL) was added dropwise to a suspension of $LiAlH_4$ (0.012 g, 0.33 mmol) in diglyme (1.0 mL) at room temperature. The resulting mixture was stirred at 130 °C, under nitrogen, for 5 h. The reaction was quenched by addition of aqueous sodium hydroxide 0.1 mol/L (2 mL) at 0 °C followed by addition of ether (10 mL). The aqueous layer was extracted twice with ether and the organic phase was dried over anhydrous sodium sulphate. The product was concentrated *in vacuo* and utilized in the next step without further purification.

To the crude product obtained as described above was added a solution of acetic anhydride and pyridine (0.2 mL, 1:2 v/v). The reaction mixture was kept under nitrogen at 0 °C for 1 h, then stirred at room temperature for 2 h. The reaction was quenched by addition of water (2 mL) followed by addition of ether (10 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent removed under vacuum. The product was purified by flash cromatography on silica gel using a mixture of hexane:ethyl acetate (20:1 ratio), yielding 66 mg (90%) of the pheromone **4**.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.39 (ddd, J = 1.21, 10.96, 15.15 Hz, 1H), 5.95 (t, J = 10.96 Hz, 1H), 5.60 (dt, J = 7.10, 15.13 Hz, 1H), 5.37 (dt, J = 7.6 Hz, 10.9 Hz, 1H), 4.11 (t, J = 6.88 Hz, 2H), 2.43 (q, J = 6.89 Hz, 2H), 2.16 (q, J = 6.89 Hz, 2H), 2.04 (s, 3H), 1.42-1.24 (m, 8H), 0.89 (t, J = 6,9 Hz, 3H); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 171.06, 131.55, 128.63, 128.24, 128.09, 63.79, 32.15, 31.74, 29.64, 28.92, 27.74, 22.62, 20.94, 14.07; **IR** (film) ν 3011, 2948, 2926, 2852, 1742, 1231, 1034 cm^{-1}; **MS** (70 eV): m/z (%)=224 (M^+, 0), 164, 107, 93, 80, 67, 43 (100).

Results and Discussion

The synthesis of (3E,5Z)-3,5-dodecadienyl acetate employing the coupling of the Z-alkenyl cuprate **1**[3,4,5] with the alkynol iodide **2**[6], the key step of the process, is outlined in Scheme 1.

The reaction of hexylmagnesium cuprate with acetylene afforded the alkenyl cuprate **1** which was coupled with 4-iodo-3-butyn-1-ol **2** with retention of the Z stereochemistry of the double bond. The enynol **3** was reduced stereoselectively with lithium aluminum hydride[7,8] in diglyme[9] affording the desired (E,Z)-dienol which was acetylated in pyridine/acetic anhydride, leading to the preparation of the pheromone in 46,8% overall yield.

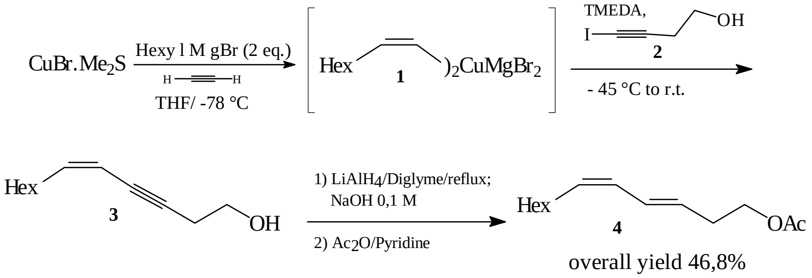
When the reduction of compound **3** with $LiAlH_4$ was quenched with a solution of HCl (conc.)[9] isomerization of the Z double bond was observed and the (3E,5E)-dienol was obtained as the main product. This isomerization was avoided by quenching the reaction with an aqueous solution of NaOH (0.1 mol/L).

The isomerization of the Z double bond of acetate **4** was also observed when this compound was kept in $CDCl_3$ solution, resulting in more than 90% of (E,E)-isomer after two weeks, as determined by ^{1}H-NMR analysis.

Conclusions

The described synthesis of the sex pheromone meets some requirements of preparative value. First, it uses low cost reagents and second it affords a product of high stereoisomeric purity with a good overall yield in a convergent approach.

The ready isomerization observed for the Z double bond of the pheromone should be taken into account when it is manipulated during field tests, in order to avoid lose of activity of this sex attractant.



Scheme 1.

Acknowledgments

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