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In memoriam prof. dr. Ioan A. Silberg

Pd(0)-CATALYZED CROSS-COUPLING REACTIONS IN THE SYNTHESIS OF (*7E,9Z*)-7,9-DODECADIENYL ACETATE, THE SEX PHEROMONE OF THE LEAF ROLLER MOTH (*Lobesia Botrana*)

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ABSTRACT. A short step synthesis of (*7E,*9Z)-7,9-dodecadien-1-yl acetate is reported. The route features are the cross-coupling reactions to assembly an enyne, which is then reduced to the desired (*E,Z*)-diene.

INTRODUCTION

Lobesia botrana is the key pest of vineyard, it presents two to five generations per year which cause a direct damage to grapes by perforating berries and an indirect damage by favoring the installation of rot fungi like *Botrytis cinerea*. The major sex pheromone of the female grape vine moth has been identified as (*7E,*9Z)-7,9-dodecadien-1-yl acetate **7** by Roelofs [1]. The compound can be used as an attractant for monitoring, through selective trapping, the population of *Lobesia botrana* in a given area. Population counts thus obtained are used in determining the frequency and quantity of spray of insecticide or other insect control agent.

During the last years, various strategies have been developed for the stereoselective construction of the conjugated diene moiety in **7** [2-7]. Among them, the Wittig-type reaction [2] and its many modifications, represents one of the most classical approach to the synthesis of **7**. An alternative to this reaction is the transition metal catalyzed C(sp)-C(sp^2) and C(sp^2)-C(sp^3) cross-coupling reactions of alk-1-yne **3** or organometallic derivatives with vinyl halogenides. This "vinyl" cross-coupling approach offers high isomeric purity of products and reasonable yields in comparison with other synthetic paths.

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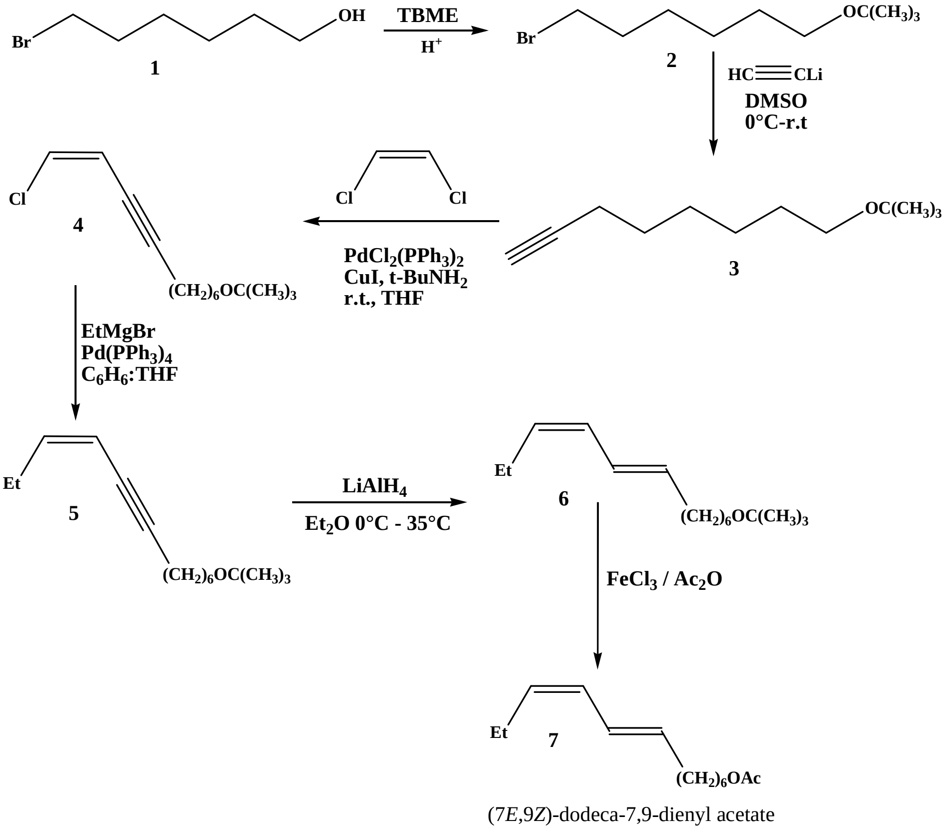
RESULTS AND DISCUSSIONS

In this paper we described a short-step synthesis of (*7E,*9Z)-7,9-dodecadien-1-yl acetate **7**, using **3**, that can be easily prepared from **2** with lithium acetilyde, as key step [8]. As shown in (Scheme 1), the cross-coupling reaction of **3** with *cis*-1,2-dichloroethylene in the presence of $PdCl_2(PPh_3)_2$, CuI and *t*-$BuNH_2$ afforded **4** in high yield and isomeric purity [9].



Scheme 1

The *Z*-chloroenynene **4** was transformed into the corresponding Z-enyne **5** by reaction with ethyl magnesium bromide in the presence of $Pd(PPh_3)_4$ in C_6H_6: THF at reflux [10]. The reduction of **5** with $LiAlH_4$ afforded **6** in good yield and isomeric purity [11]. The structural analysis of the synthesized compounds was carried out using GC-MS and NMR investigations.

CONCLUSIONS

A new method for the construction of the required carbon chain with a conjugated diene moiety in **7** is described, based on the Pd catalyzed cross-coupling reactions. Stereoisomeric purity of **7** was higher than 95% (GC). Overall yield was 19% based on the starting 6-bromohexan-1-ol.

EXPERIMENTAL PART

^{1}H-NMR (300 MHz) spectra were recorded at *rt* in C_6D_6 on a Bruker 300 MHz spectrometer, using the solvent line as reference. Electron impact (70 eV) mass spectra were obtained on Hewlett-Packard MD 5972 GC-MS instrument. GC analyses were performed on a Hewlett-Packard HP 5890 gaz cromatograph. A HP-5MS capillary column (30 m x 0.25 mm x 0.33 µm) and helium gas were used for separations.

All chemical reactions were run in dried glassware under nitrogen atmosphere. THF and DMSO were used as purchased. Pd catalysts were prepared as described in the literature[10].

1-Bromo-6-(*tert*-butoxy)hexane 2

The compound **2** was prepared by a standard manner from 6-bromohexan-1-ol (40.0 g, 0.22 mol) in the presence of catalytic amount of H_2SO_4 in *t*-butyl-methyl-ether as solvent. Yield 90%, (47 g). $C_{10}H_{21}BrO$. Mol. Wt.: 237.18. **^{1}H-NMR** (300 MHz, C_6D_6 , δ ppm): 3.19-3.15 (2H, t, J = 6.3 Hz, $-CH_2-Br$), 2.95-2.91 (2H, t, J = 6.7 Hz, $-CH_2$-OtBu), 1.5-1.17 (m, 8 H), 1.17 (9H, s).

8-(*tert*-Butoxy)oct-1-yne 3

To a stirred and cooled (0 ºC) suspension of lithium acetylide-ethylenediamine complex (2.52 g, 0.042 mol) in anhydrous dimethyl sulfoxide (25 mL) was slowly added compound **2** (5 g, 0.021 mol). The reaction mixture was stirred at room temperature for 6 h, then it was poured into ice water and extracted with hexane (4 x 25 mL). The combined hexane extracts were washed with water (3 x 25 mL), brine (2 x 25 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the oily residue was used further without purification. Yield 91%, (3.5 g). $C_{12}H_{22}O$. Mol. Wt.: 182.3. **^{1}H-NMR** (300 MHz, C_6D_6 , δ ppm): 3.21-3.17 (2H, t, J = 6.3 Hz, $-CH_2$-OtBu), 1.95-1.93 m (2H, m, $-CH_2-C\equiv$), 1.78-1.76 (1H, t, J = 2.7 Hz, $-C\equiv H$), 1.48-1.23 (8H, m), 1.10 (9H, s).

(*Z*)-10-*tert*-Butoxy-1-chlorodec-1-en-3-yne 4

A mixture of $PdCl_2(PPh_3)_2$ (0.3 g, 0.5 mmol, 0.05 % eq.), (*Z*)-1,2-dichloroethene (3.34 g, 0.034 mol), terminal alkyne **3** (2.1 g, 0.0115 mol) and *t*-butylamine (1.68 g, 0.023 mol) in absolute THF was stirred for 15 min. at room temperature under nitrogen atmosphere, and CuI (0.2 g, 1.15 mmol) was then added.

The stirring was continued until TLC analysis indicated complete consumtion of the alkyne. The reaction mixture was treated with a saturated solution of $NaHCO_3$ and extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by column chromatography, using CH_2Cl_2 : petroleum ether = 1 : 1 as eluent, to yield the desired chloroenyne. Yield 72%, (2.0 g). $C_{14}H_{23}ClO$. Mol. Wt.: 242.78. ^{1}**H-NMR** (300 MHz, C_6D_6 , δ ppm): 5.73-5.71 (1H, d, J = 7.3 Hz, Cl-C**H**=), 5.48-5.45 (1H, m, Cl-CH=C**H**-), 3.22-3.17 (2H, t, J = 6.3 Hz, -CH_2OtBu), 2.11-2.09 (2H, m, -CH_2-CH=), 1.55-1.11(8H, m), 1.11 (9H, s).

(*Z*)-1-*tert*-Butoxydodec-9-en-7-yne 5

To a mixture of $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol) and chloroenyne **4** (1.0 g, 4.12 mmol) in benzene : THF = 1 : 1 under nitrogen atmosphere was added dropwise a solution 1M in THF of EtMgBr (6.2 mL) at 0 ºC. The resulting dark brown reaction mixture was then refluxed for 8 h. The reaction mixture was diluted with diethyl ether (50 mL) and quenched with 2N HCl. The layers were separated and the aqueous layer was extracted with diethyl ether; the combined organic layers were washed with saturated brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the product was purified by column chromatography using CH_2Cl_2 : petroleum ether = 1 :1 as eluent to afford **5**. Yield: 41 % (0.4 g). $C_{16}H_{28}O$. Mol. Wt.: 236.39. ^{1}**H-NMR** (300 MHz, C_6D_6 , δ ppm): 5.67-5.59 (1H, m, -CH_2-C**H**=), 5.56-5.49 (1H, m, -CH=C**H**-), 3.22-3.18 (2H, t, J = 6.7 Hz, -C**H**$_2$-CH_3), 2.19-2.11 (2H, m), 1.32-1.29 (6H, m), 1.10 (m, 2H), 1.10 (9H, s), 0.93-0.88 (3H, t, J = 7.5 Hz, -CH_2-C**H**$_3$).

(*7E,9Z*)-1-*tert*-Butoxidodeca-7,9-diene 6

To a suspension of lithium aluminum hydride (32 mg, 0.83 mmol) in diethyl ether (10 mL) at -5 ºC under nitrogen atmosphere was added a solution of 5 (0.4 g, 1.7 mmol) in diethyl ether (10 mL) dropwise over a period of 15 min. The reaction mixture was stirred for 2 h at 35 ºC and then cooled to 0 ºC.

The reaction mixture was diluted with diethyl ether (20mL) and quenched with 2N HCl. The layers were separated and the aqueous layer was extracted with ether; the combined organic layers were washed with saturated brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo. The product was purified by column chromatography using CH_2Cl_2 : petroleum ether = 1 : 1 to afford **6**. Yield: 70% (0.28 g). $C_{16}H_{30}O$. Mol. Wt.: 238.41. ^{1}**H-NMR** (300 MHz, C_6D_6 , δ ppm): 6.39-6.34 (1H, m), 6.05-5.95 (1H, m), 5.63-5.54 (1H, m), 5.30-5.28 (1H, m), 3.94-3.90 (2H, t, J = 7.5 Hz, -C**H$_2$**-CH=), 2.12-2.06 (2H, m, -C**H$_2$**-CH_3), 1.30-1.26 (6H, m), 1.09 (11H, m, s), 0.92-0.87 (3H, t, J = 7.5 Hz, -CH_2-C**H$_3$**).

(*7E,*9Z)-7,9-Dodecadien-1-yl acetate 7[8]

To a solution of protected alcohol **6** (0.28 g, 1.18 mmol) in diethyl ether was added acetic anhydride (1 mL), and then anhydrous $FeCl_3$ (18 mg, 0.11 mmol). The dark brown solution was stirred for 20 h at room temperature. A saturated aqueous solution of Na_2PO_4 (10 mL) was added, and the mixture was stirred for 2 h. The solid $FePO_4$ was filtered off, and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The collected organic phases were dried over anhydrous $MgSO_4$ and then concentrated. The red oily residue was further purified on column chromatography to afford **7** using CH_2Cl_2 : petroleum ether = 1 : 1. Yield 80% (0.2 g). $C_{14}H_{24}O_2$. Mol. Wt.: 224.34. **^{1}H-NMR** (300 MHz, C_6D_6 , δ ppm): 6.41-6.36 (1H, m), 6.09-6.01 (1H, m), 5.62-5.54 (1H, m), 5.33-5.29 (1H, m), 3.96-3.92 (2H, t, J = 6.7 Hz, -C**H$_2$**-CH=), 2.14-2.09 (2H, m, -C**H$_2$**-CH$_3$), 1.99-1.97 (2H, m), 1.68 (5H, m), 1.68 (5H, m+s), 1.38-1.10 (6H, m), 0.93-0.88 (3H, t, J = 7.6 Hz, -CH$_2$-C**H$_3$**).

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