# Synthesis of E-9-Dodecen-1-yl Acetate Using Organomanganese Reagents

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The Grignard reagent obtained from 2-(6-bromohexyloxy)-tetrahydropyrane, by treatment with anhydrous manganese(II) chloride was transformed to the corresponding organomanganese reagent, which was coupled with E-1-bromo-3-hexene by treatment with anhydrous manganese chloride. Further deprotection and acetylation furnished E-9-dodecen-1-yl acetate. A second procedure involved the coupling of E-3-hexenylmanganese bromide and 6-bromohexyl acetate. Coupling reactions were carried out at 0 °C, using tetrahydrofurane and N-methylpyrrolidone as co-solvent.

# Introduction

In Chile the pine shoot moth (*Rhyacionia buoliana*) was first detected in 1985, since then the population of this insect has spread out in such an extent that it has become the main forest pest in our country. Nowadays it covers about 90% of the pine planted area. There are 1,380,000 hectares planted with pine that account for 75% of the forest plantations. Productivity losses up to 15% of the total amount of wood at the moment of harvesting have been measured. These losses are due to the tree malformation that result as a consequence of the insect attack.

We are currently studying the potential of using the sex pheromone to control the pine shoot moth and in this context it is interesting to study new methods to obtain its components: E-9-dodecenvl acetate and E-9-dodecen-1-ol [1]. Since these chemicals are imported and very expensive, we are interested in reactions that would allow obtaining big amounts of them. Our future goal is a pilot plant scale. Classical methods to carry out the synthesis of compounds like E-9-dodecen-1-yl acetate are the acetylenic route [2] and the Wittig reaction [3]. The first one seems to be the best suited for largescale synthesis, however, in order to achieve very high yields, hexamethylphosphoryltriamide must be used as a co-solvent. This chemical is very toxic and expensive. The second drawback of this reaction is that very low temperature is required, -78 and -30 °C. In the Wittig reaction, the main problems

became the triphenylphosphine oxide that is obtained as a by-product and renders the purification of the target compound more difficult, and the presence of some Z-isomer that makes the mixture unsuitable for biological purposes [4].

Coupling reactions using organomanganese(II) reagents reported in recent years [5 - 7] show high yields with temperature conditions which are easily achievable. This result prompted us to try such kind of reagents to synthesize E-9-dodecen-1-yl acetate and the results are here reported.

### **Results and Discussion**

The first route is outlined in Scheme 1. E-1bromo-3-hexene (2) was prepared from commercial E-3-hexen-1-ol (1) that was added to freshly prepared dibromotriphenylphosphorane. On the other side, monobromination of 1,6-hexanediol (3) with 47% aqueous HBr afforded 6-bromo-hexan-1-ol (4) that was protected by preparing the tetrahydropyranyl ether (5). Compound 5 was used to prepare the Grignard reagent (6), which by addition of anhydrous manganese(II) chloride was transformed to the organomanganese reagent (7). Coupling of 7 with E-1-bromo-3-hexene in the presence of CuCl<sub>2</sub> and LiCl as catalysts and NMP as cosolvent, yielded compound 8 that was hydrolyzed and then acetylated to obtain E-9-dodecen-1-yl acetate (10).

It is also reported [6] that organomanganese(II) reagents do not react with acetates. Therefore we

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decided to try the synthesis of E-9-dodecen-1-yl acetate following the route outlined in Scheme 2. By this method the use of expensive dihydropyrane could be avoided and replaced by acetic anhydride. Treatment of 6-bromo-hexan-1-ol (4) with acetic anhydride afforded the acetate 11, subsequent coupling with E-3-hexenyl manganese bromide (13) gave 10. This order was followed because 6-bromohexyl acetate does not form a Grignard reagent and therefore no organomanganese derivative can be obtained from it.

The routes described are characterized by very high yields, however, the second one seems more interesting to us, because the acetate is immediately obtained and with fewer steps. Although some acetate hydrolysis was observed, this is not a big problem because the alcohol and the acetate can readily be separated through a silica column. Furthermore, E-9-dodecen-1-ol is the second pheromone component [1] in *R. buoliana*. The starting E-3-hexen-1-ol used was commercially available, but it can also be prepared as described in the literature [8].

#### Experimental

The compounds were characterized using <sup>1</sup>H, <sup>13</sup>C NMR spectroscopy (Bruker AC 250P; 62.9 and 250 MHz, respectively). In all the cases the solvent was deuteriated chloroform.

### Synthesis of E-1-bromo-3-hexene (2)

In a two necked flask fitted with a reflux condenser (with a CaCl<sub>2</sub> tube on top) and a dropping funnel, triphenylphospine (230.0 g; 0.88 mole) is dissolved in methylene chloride. The solution is cooled to 0 °C and more solvent is added if some crystallization is observed. To the stirred solution, bromine (40.98 ml, 0.80 mole) is



dropped. A pale yellow precipitate appears at the end of the addition. Stirring is continued while allowing the mixture to warm up to r. t., and then E-3-hexen-1-ol (50.0 g, 0.5 mole) is added dropwise. The solid material dissolves and stirring is continued for 12 h. The solution is then saturated with pentane to precipitate any unreacted phosphorane and triphenylphosphine, and then filtered. The solution is washed with aqueous 10% NaHCO<sub>3</sub> and then with methanol containing 10% of water to eliminate the remaining triphenylphosphine oxide. The hexane phase is dried over sodium sulfate. After filtering, the solvent is removed by normal distillation. The remaining crude is distilled with water pump vacuum and the fraction between 73 - 76 °C collected. Yield 89% (67 g).

<sup>1</sup>H NMR: 5.5 (m, m, 2H, =CH), 3.99 (t, 2H, 6.3 Hz, CH<sub>2</sub>Br), 2.59 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Br), 2.07 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.05 (t, 3H, 8.6 Hz, CH<sub>3</sub>).

<sup>13</sup>C NMR: 135.4 (1C, C-3), 125.4 (1C, C-4), 36.0, 32.9 (2C, C-3 and C-4), 25.5 (1C, C-1), 13.6 (1C, C-6).

### Synthesis of 6-bromohexan-1-ol (4)

In a flask provided with a reflux condenser and a mechanical stirrer, a mixture of 1,6-hexanediol (100 g; 0.85 mole), 46% aqueous HBr (600 ml; 5.08 mole) and hexane (300 ml) is heated to reflux for 2 h. The mixture is allowed to cool down to r. t. and the phases are separated. The aqueous phase is neutralized with solid NaHCO<sub>3</sub> and extracted three times with ether. The collected organic extracts are dried with sodium sulfate. After filtering,

the solvent is removed in a rotatory evaporator and the crude distilled in a water pump vacuum. The fraction collected between 75 - 80 °C is 6-bromohexan-1-ol. Yield 65% (100 g).

<sup>1</sup>H NMR: 3.59 (t, 2H, CH<sub>2</sub>O-), 3.45 (s, 1H, OH), 3.40 (t, 6.3 Hz, 2H, CH<sub>2</sub>Br), 1.87 (q, 2H, CH<sub>2</sub>), 1.62-1.30 (m, m, 6H, 7.5 Hz, 3CH<sub>2</sub>).

<sup>13</sup>C NMR: 62.1 (1C, CH<sub>2</sub>OH), 33.6, 32.5, 32.1, 27.7, 24.7 (5C, CH<sub>2</sub>).

#### Synthesis of 2-(6-bromohexyloxy)tetrahydropyrane (5)

A mixture of 6-bromohexan-1-ol (10 g, 0,07 mole) and dihydropyrane (6.47 g, 0.77 mole) and some drops of trifluoroacetic acid are stirred for 12 h at r. t.. The solution is washed with saturated aqueous sodium carbonate, and then with water until pH 7. The organic phase is dried over sodium sulfate and filtered. The filtrate is concentred in a rotatory evaporator to eliminate the unreacted dihydropyrane. At this stage the yield is 85%. This product is used in the next step without further purification.

<sup>13</sup>C NMR: 98,6 (C-1, acetal), 67.2, 62.6 (2C, CH<sub>2</sub>O), 33.6, 32.5, 30.7, 29.3, 27.8, 25.3, 19.5 (8C, 8CH<sub>2</sub>).

#### Synthesis of E-2-(9-dodecenyloxy)tetrahydropyrane (8)

This reaction is carried out under nitrogen atmosphere. To a three necked flask containing magnesium turnings (24.3 g, 0.05 mole) and sodium dried THF, a solution of 5 (7.39 g, 0.045 mole) in 15 ml of THF is added dropwise. Starting of the reaction is promoted by adding some drops of 1,2-dibromoethane. After the metal is dissolved, stirring is continued for 30 min. The solution is cooled to 0 °C and anhydrous manganese(II) chloride (5.91 g, 0.047 mole) dissolved in THF (15 ml) is added at once. The mixture is stirred for 12 h at r.t. and then bromide 2 (6.11 g, 0.038 mole) and 35 ml of NMP are added together with a solution of  $CuCl_2$  (0.28 g) and LiCl (0.17 g) in THF (20 ml). The solution is stirred for 6 h. The reaction is quenched adding water and neutralized with 10% aqueous HCl. THF evaporated in a rotatory evaporator and the remaining mixture is extracted three times with hexane. The collected organic extracts are dried with sodium sulfate and filtered. The solvent is evaporated and the product chromatographed on a silica gel column (hexane : ethyl ether, 90 : 10). Yield: 70% (6 g).

<sup>13</sup>C NMR: 131.3, 129.2 (2C, =CH), 98.8 (1C, acetal CH), 67.3 62.3 (2C, CH<sub>2</sub>0), 33.7, 32.7, 31.5, 30.7, 29.5, 28.0, 25.4, 22.57, 19.63 (10C, CH<sub>2</sub>), 14.0 (1C, Me).

# Synthesis of E-9-dodecen-1-ol (9)

Compound 8 (5.0 g, 0.019 mole) is dissolved in methanol (10 ml). A few of trifluoroacetic acid are added and the solution is stirred at r. t. and then concentrated in a

rotatory evaporator and diluted with ether. The new solution is washed three times with saturated aqueous sodium bicarbonate and then with saturated acqueous NaCl until pH 7. The organic phase is dried with sodium sulfate and filtered, and the solvent is evaporated. The crude is chromatographed on a silica column (hexane : ethyl ether, 90 : 10). Yield 78% (2.7 g).

<sup>1</sup>H NMR: 5.42 (m, 2H, =CH), 3.59 (t, 7.5 Hz, 2H, CH<sub>2</sub>0), 3.23 (s,1H, OH), 2.01 (m, 4H), 1.54 (m, 2H), 1.31 (s, broad, 10H), 0.97 (t, 6.8 Hz, 3H, Me).

<sup>13</sup>C NMR: 131.7, 129.1 (2C, =CH), 62.4 (1C, OCH<sub>2</sub>), 32.6, 32.4, 29.5, 29.4, 29.3, 29.0, 25.7, 25.4 (8C, CH<sub>2</sub>), 13.8 (1C, Me).

# Synthesis of E-9-dodecen-1-yl acetate (10)

Route A: A solution of E-9-dodecen-1-ol **9** (2.5 g, 0.014 mole), acetic anhydride (10 ml), pyridine (10 ml), and some crystals of 4-dimethylaminopyridine is stirred for 12 h at r. t.. The solution is diluted with ether, cooled with ice, then treated with 10% HCl until the pH is acid, and washed with saturated acqueous NaCl until pH 7. The organic phase is dried over sodium sulfate and filtered, and the solvent is evaporated. The crude is purified through a silica column (hexane : ethyl ether, 98 : 2). Yield 94% (3 g).

<sup>1</sup>H NMR: 5.42 (m, 2H, =CH), 4.05 (t, 6.3 Hz, 2H, OCH<sub>2</sub>), 2.04 (s, 3H, CH<sub>3</sub>CO), 1.01 (m, 4H, 2CH<sub>2</sub>), 1.62 (m, 2H, CH<sub>2</sub>), 1.30 (s, broad, 10H, 5CH<sub>2</sub>), 0.96 (t, 7.5 Hz, 3H, CH<sub>3</sub>).

<sup>13</sup>C NMR: 171,1 (1C,C=), 131.9, 129.2 (2C, =CH), 64.6 (1C, OCH<sub>2</sub>), 32.5, 29.6, 29.3, 29.2, 29.0, 28.6, 25.9, 25.5 (8C, CH<sub>2</sub>), 20.9 (1C, CH<sub>3</sub>CO), 13.9 (1C, CH<sub>3</sub>).

### *Synthesis of 6-bromohexyl acetate* (11)

The same procedure described for **10** is followed. 6-Bromohexan-1-ol **4** (50 g, 0.383 mole), 100 ml of acetic

anhydride and 100 ml of pyridine and a small ammount of dimethylamino- pyridine are used. Yield 98% (5.8 g).

<sup>1</sup>H NMR: 3.96 (t, 6.6 Hz, 2H, CH<sub>2</sub>O), 3.31 (t, 6.9 Hz 2H, CH<sub>2</sub>Br), 1.95 (s, 3H, CH3), 1.77 (q, 2H, CH<sub>2</sub>), 1.35 (m, 4H, 2CH<sub>2</sub>).

<sup>13</sup>C NMR: 170.6 (1C, C=O), 64.0 (1C, CH<sub>2</sub>O), 33.3, 32.2, 28.1, 27.4, 25.2, 24.8 (5C, CH<sub>2</sub>), 20.6 (1C, Me).

#### Synthesis of E-9-dodecenyl acetate (10)

Route B: This reaction is carried out under nitrogen atmosphere. To a flask containing magnesium turnings (24.31 g, 0.051 mole) and dried THF, E-1-bromo-3hexene (7.34 g, 0.045 mole) dissolved in 15 ml of THF are added dropwise. The mixture is stirred for 6 h after the magnesium has dissolved. To this flask a solution of MnCl<sub>2</sub> (5.91 g, 0.047 mole) in 15 ml of THF is slowly dropped keeping the temperature between 0 and 5 °C with an ice bath. After the addition the solution is for during 12 h and then transferred with a double tipped-needle to a flask containing 6-bromohexenyl acetate (8.37 g, 0.038 mole) in THF. To the new solution NMP (35 ml) is added and LiCl (0.11 g) and CuCl<sub>2</sub> (0.19 g) in THF (15 ml) are slowly dropped so that the reaction temperature does not rise. Stirring is continued for 6 h. The solution is again cooled with an ice bath and the reaction quenched by adding water and then 10% aqueous HCl until the pH is neutral. The solvent is evaporated in a rotatory evaporator. The remaining mixture is extracted three times with hexane. The collected hexane extracts are dried over sodium sulfate and filtered, and the solvent is evaporated. The crude is chromatographed on a silica column (hexane : ethyl ether, 70 : 30). Yield 57% (4.9 g).

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