

Unsymmetrical double Wittig olefination on the syntheses of insect pheromones. Part 1: Synthesis of 5,9-dimethylpentadecane, the sexual pheromone of *Leucoptera coffeella*

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Abstract—An expeditious three-step synthesis of a mixture of stereoisomers of 5,9-dimethylpentadecane **1**, the sexual pheromone of the coffee leaf miner *Leucoptera coffeella*, is described. The route employs an unsymmetrical double Wittig olefination to build the carbon skeleton of the molecule, as the key reaction. The bis-phosphonium salt **3**, derived from 1,3-dibromopropane **2**, reacted ‘one-pot’ with the ketones 2-octanone and 2-hexanone, affording the asymmetric diene **4**. This was readily hydrogenated over Pd/C, furnishing pheromone **1** in 54% overall yield. Synthetic **1** showed high biological activity when tested in field experiments.
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Natural products with a 1,5-dimethyl branched pattern are commonly isolated from a large variety of sources.¹ As an example, several insect pheromones² and insect cuticular hydrocarbons³ have been described with this structural characteristic. The compound 5,9-dimethylpentadecane **1** (Fig. 1) was identified by Francke et al.⁴ as the sexual pheromone of the coffee leaf miner *Leucoptera coffeella*. This species is one of the most important pests on coffee in Brazil, and is also found in other countries in South America.⁵

Few examples of racemic or stereoselective syntheses of compound **1** have been described in the literature.^{4,6,7}

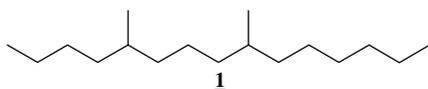


Figure 1.

Keywords: Pheromone; Synthesis; 5,9-Dimethylpentadecane; *Leucoptera coffeella*; Double Wittig reaction; 7,11-Dimethylheptadecane; 7-Methylheptadecane; Cuticular hydrocarbons.

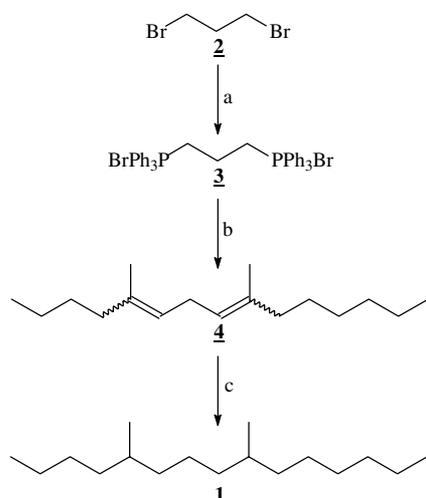
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Recently, a total synthesis of all of the four possible stereoisomers of **1** was published by Kuwahara et al.⁸

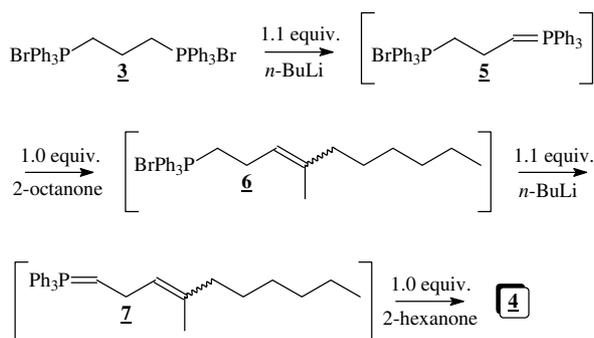
The absolute configuration of the natural pheromone still remains to be determined. One of us (E.R.L.)⁹ observed that the (5*S*,9*S*) isomer of **1** elicited higher antennal response in EAD experiments when compared with the other three possible isomers. However, in field experiments, traps baited with pure isomers were poor attractive. The insects were equally attracted only to a binary mixture of the (5*S*,9*S*) and (5*R*,9*S*) isomers, and to a stereoisomeric mixture of **1**.⁹

Here we report an expeditious three-step synthesis of a mixture of stereoisomers of 5,9-dimethylpentadecane **1**, employing an unsymmetrical double Wittig olefination as the key reaction (see Scheme 1), and the biological activity of this synthetic pheromone in field experiments.

The bis-phosphonium salt **3** was readily synthesized in large scale from 1,3-dibromopropane **2** in DMF¹⁰ (the precipitation of the mono salt is observed when a less polar solvent is employed) and can be stored indefinitely. The asymmetric diene **4** was obtained one-pot through addition of 1.0 equiv of 2-octanone to the monoyleide **5**, generated from symmetric bifunctional salt **3**, followed by the addition of 1.0 equiv of 2-hexanone



Scheme 1. Synthesis of the pheromone **1**. Reagents and conditions: (a) 2.1 equiv PPh_3 , DMF, 92%; (b) (i) 1.1 equiv $n\text{-BuLi}$, -90°C , (ii) 1 equiv 2-octanone, -90°C to room temperature, (iii) 1.1 equiv $n\text{-BuLi}$, -90°C , (iv) 1 equiv 2-hexanone, -90°C to room temperature, 64%; (c) Pd/C, hexane, H_2 (30 psi), 93%.



Scheme 2.

to the new mono-ylide **7**, derived from intermediate **6** (see Scheme 2). Under optimized reaction conditions,¹¹ the formation of the symmetrical by-products **4a** and **4b** was less than 10% of the product mixture (Fig. 2A). Since the target molecule of the present work is a saturated compound, no efforts were made in order to control the geometry of the double bonds. In this reaction, both ylides **5** and **7** were generated employing 1.1 equiv of $n\text{-BuLi}$ as base, at -90°C . Finally, a routine hydrogenation over Pd/C of dienes afforded pheromone **1** as a mixture of stereoisomers, in 54% overall yield. The ratio of the hydrogenated by-products **1a** and **1b** was the same as detected to the dienes (Fig. 2B).

We employed successfully the same approach on the synthesis of two others saturated hydrocarbons identified as components of the female sex pheromone of the spring hemlock looper *Lambdina athasaria*¹² the 7,11-dimethylheptadecane **1b** and 7-methylheptadecane **8**.¹³ Symmetric **1b** could be easily prepared in excellent yields (65%) using only 2-octanone to react with the ylides **5** and **7**, while the single methyl branched compound **8** was obtained in 49% overall yield employing 2-octanone and heptanal¹³ as carbonyl sources.

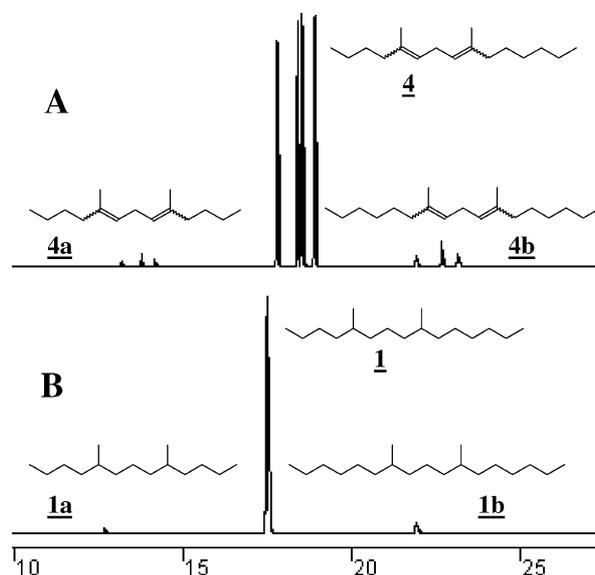


Figure 2. (A) GC profile of the stereoisomeric mixture of the dienes. Products ratio **4/4a/4b** ~ 1.0:0.028:0.070; (B) GC profile of the saturated hydrocarbons.

A sequential double-Wittig reaction was previously described by Pohnert et al.¹⁴ and Pohnert and Boland¹⁵ on the synthesis of homoconjugated trienes as volicitin, a potent elicitor of plant volatile biosynthesis,¹⁶ and geometrid moth pheromones. In that case, the authors reacted the carbonyl compounds with a bis(ylide) generated from the addition of 2.2 equiv of $\text{KN}(\text{SiMe}_3)_2$ (allowing to ensure a (*Z*)-configuration of the resulting double bonds¹⁷) to an unsaturated symmetric bifunctional Wittig salt. However, in our modified experiments,¹¹ we detected that by reacting the first carbonyl compound (ketones or aldehydes) with a mono-ylide, as structure **5**, and further generating the new reactive ylide, as structure **7**, the formation of symmetric coupling products could be suppressed in almost 20%.

We suppose that the formation of one phosphorane at a time is possible due to the stability of anions under different temperature, that is, after addition of the first equivalent of $n\text{-BuLi}$ at -90°C , statistical mixture of the bisphosphorane and monophosphorane must be formed. However, when the reaction reached room temperature, keep stirring for an additional time, the bis(ylide) must be converted to the mono-ylide by reacting with the remaining bis-Wittig salt. This hypothesis is supported on the fact that when the carbonyl sources were added to the phosphoranes that were not previously heated, ~45% of the symmetric coupling dienes **4a** and **4b** were obtained.

Field experiments were run on coffee plantations in Viçosa MG, Brazil, to test the biological activity of synthetic **1**. Rubber septa (8 mm OD, white rubber, Aldrich) were loaded with 0.5 mg of synthetic **1** and with a racemic pheromone provided by Fuji Flavors (Japan).¹⁸ Delta traps (10/treatment) were positioned randomly 30 m apart from each other in the field. Traps were placed at 0.1 m above the ground. Moths trapped

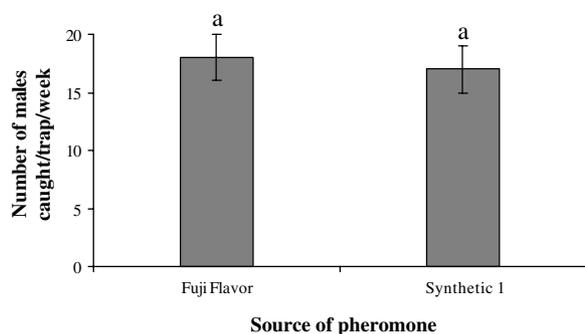


Figure 3. Number (mean \pm SE) of *L. coffeella* males caught in Delta traps baited with different pheromone sources during 7 weeks. The amount of components loaded in each rubber septum was 0.5 mg (10 replicates).

were counted every week during 7 weeks. After each counting, insects were removed. The lures were placed at the bottom of the traps.⁹

Male attraction was not significantly different among the traps baited with our synthetic **1** and with the Fuji Flavors pheromone ($F_{1,133} = 0.033$; $p = 0.8554$). The means of trap catch per week is represented in Figure 3.

In summary, we have straightforward synthesized a stereoisomeric mixture of hydrocarbons pheromones and tested the biological activity of 5,9-dimethylpentadecane **1**. Field experiments revealed that the synthetic pheromone, as appear in Figure 2B,¹⁹ was highly attractive to males *L. coffeella*. We are now synthesizing other insect pheromones employing this methodology, including optically active molecules, and the results will appear in due course.

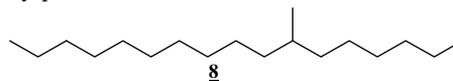
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- Typical procedure for the double-Wittig reaction: To a cold $-90\text{ }^{\circ}\text{C}$ (ethanol/liquid N_2 cooling bath) suspension of the bis-phosphonium salt (1.0 mmol) in THF (10 mL) was added *n*-BuLi (1.1 mmol, 2.0 mol L^{-1} in hexane), and the reaction mixture was allowed to warm to room temperature, stirred for additional 30 min and re-cooled ($-90\text{ }^{\circ}\text{C}$). A solution of the first carbonyl component (1.0 mmol) in THF (1.0 mL) was added dropwise, and the mixture was allowed to reach room temperature, stirred for additional 30 min and re-cooled ($-90\text{ }^{\circ}\text{C}$). The same protocol was adopted to generate the second ylide (1.1 equiv *n*-BuLi) and to the addition of the second carbonyl component (1.0 equiv). Usual work-up and flash chromatography on silica gel yielded the respective dienes.
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- The reactivity of ketones and aldehydes with the mono-ylides under the reaction condition described above is quite similar, and the ratio of the symmetric coupling by-products obtained is almost the same



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- This compound was proved as highly efficient in capturing males of coffee leaf miner in the field. The manuscript is in preparation.
- It is quite difficult to separate the symmetrical products **1a** and **1b** to the unsymmetrical **1** by conventional methods. However, in the cases that the carbonyl sources differs in more than four carbon atoms, a carefully distillation allow the purification.