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An easy and adjustable one-pot access to pheromonal blends of fall armyworm (*Spodoptera frugiperda*) relying on a key ligand- and additive-free iron-catalyzed cross-coupling.

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Supporting Information Placeholder

ABSTRACT: We describe in this report a convenient convergent synthesis of the pheromonal blend of *Spodoptera frugiperda*, relying on a key ligand- and additive-free iron-catalyzed cross-coupling operating at a low 0.1 mol% catalytic charge. This approach relies on the use of the same electrophilic partner for the preparation of the three components of the blend, which can be prepared altogether in a single step with a 94% isolated yield. Overall, the pheromonal blend is obtained with a 61% yield at a 20 g scale, with an accurate control of the distribution of its three components.

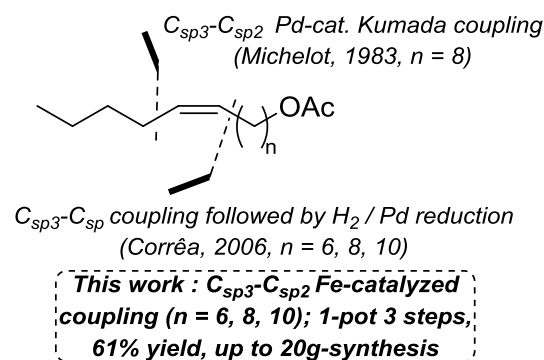
Keywords: pheromones, cross-coupling, iron catalysis, Grignard reagents

INTRODUCTION

The use of pesticides keeps causing significant ecological issues, as some of those compounds may impact human health and ecosystems. To circumvent this matter, bio-control based on use of insect sex pheromones stands as an eco-friendly solution to protect crops, plants or vineyards,^{1a} especially given that those compounds are totally biodegradable, specific to the targeted species, and with no toxicity to human health.^{1b} In order to pursue our efforts in the development of efficient and reliable synthetic procedures to access a large variety of insect pheromones applied to biological control, we focused our interest on the synthesis of the sex pheromone of fall armyworm (*Spodoptera frugiperda*), a lepidoptera whose populations cause significant harm to several crops such as rice or corn fields, as well as sugar cane.^{2a,b} Originally located in tropical areas of South America, populations of fall armyworms have spread worldwide in the late 2010s,^{2c,d} leading to considerable economic damages in the infested zones.^{2e}

In order to develop bio-controlled solutions for the protection of the aforementioned crops from this specific pest, an accurate knowledge of the composition of its pheromone is essential. Composition of fall armyworm pheromone proved to be a mixture of at least two compounds (Scheme 1, $n = 6, 8$): 9Z-tetradecen-1-yl acetate (**Z9-14:Ac**, major, $n = 8$) and 7Z-dodecen-1-yl acetate (**Z7-12:Ac**, minor, $n = 6$).^{3a} Interestingly, a third component is often observed in this blend, with strong intraspecific geographical variations. For example, 9Z-dodecen-1-yl acetate (**Z9-12:Ac**) is observed in Guianese populations,^{3b} whereas E7-dodecen-1-yl acetate (**E7-12:Ac**) is only detected in Brazilian species.^{3c} On the other hand, Z11-hexadecen-1-yl acetate (**Z11-16:Ac**, Scheme 1, $n = 10$) is

Scheme 1. Structure of components of *Spodoptera frugiperda* sex pheromone ($n = 6, 8, 10$); reported synthetic strategies, and strategy developed in this work to access the overall pheromone.



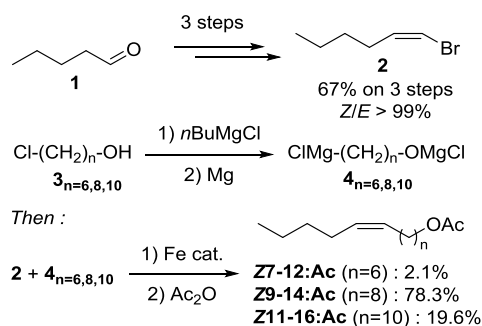
detected in significant quantities (10-20% of the overall mixture) in all species from American continent.^{3d} Moreover, *Spodoptera frugiperda* pheromonal blend dosage used in commercial biocontrol requires a small quantity of finished products : less than 0.04 kg per hectare per application (vs 3.4 kg of conventional pesticides per hectare), making it particularly interesting from an ecological standpoint.^{3e} As a representative mixture of interest, we aimed at developing a method ensuring an easy and scalable access to a blend of (**Z7-12:Ac**)/(**Z9-14:Ac**)/(**Z11-16:Ac**) in a 2.1/78.3/19.6 ratio, a choice guided by a first report by Meagher and Mitchell as well as more recent studies by Oehlschlager (Scheme 1, $n = 6, 8, 10$).^{3f-g}

After the identification of the components of the pheromone in the 1970s, a synthesis of the major compound **Z9-14:Ac**

was reported by Michelot in 1983.^{4a} This linear 8-step synthesis operates with a 17% yield, the key step being the introduction of the C₁₀-C₁₁ linkage by a Pd-catalyzed Kumada cross-coupling between an aliphatic Grignard reagent and a vinyl iodide. Preparation of the latter synthon moreover involves use of highly reactive acetylide HC≡CLi in the described procedure, as well as further reduction of the alkynyl group with a diazene precursor. Corrêa also reported in 2006 a method allowing the synthesis of the three components of the pheromone (n = 6, 8, 10). In that case, the lateral C₆ chain is derived from 1-hexyne, reaction of lithium salt of the latter with α,ω-bromoalcohols followed by reduction with H₂ on Lindlar Pd affording the targeted compounds.^{3c} This 4-step method provides for example **Z9-14:Ac** in a 58% yield and >99% stereoselectivity. It is of note that synthetic procedures by yeast fermentation were also reported recently.^{4b} It however appears that reported syntheses of components found in *Spodoptera frugiperda* pheromone so far involve either linear procedures with numerous steps and a low overall atom economy, expensive Pd-catalyzed steps, as well as a requirement of hazardous chemicals such as acetylides salts, diazene precursors, or H₂-based reductions. Because of that, such processes may be difficultly extended to high-scale syntheses, e.g. requiring specific equipment withstanding high pressures.

During the last few years, we demonstrated that introduction of insaturations in linear pheromones could easily be done using an iron-catalyzed cross-coupling between alkyl Grignard reagents and alkenyl electrophiles in the absence of any cosolvent or ligand.⁵ The key of this approach is to use α,ω-difunctionalized Grignard reagents bearing a magnesium alkoxide terminal group (-OMgX). Synthesis of such compounds is moreover possibly carried out at a ton scale synthesis in our facilities, making it appealing for scalable processes. This functionalization enables a kinetic stabilization of organoiron(II) species, which are key intermediates of the coupling process.⁶ Inspired by this previous work, we sought to develop a convenient synthesis of the sex pheromone of *Spodoptera frugiperda* relying on a key iron-catalyzed cross-coupling between 1Z-hexenyl bromide (**2**, readily obtained from pentanal **1**) and a mixture of α,ω-difunctionalized Grignard reagents bearing terminal alkoxide groups (**4**_{n=6}, **4**_{n=8} and **4**_{n=10}, Scheme 2). Our idea is to use a mixture of α,ω-chloroalcohols as starting reagents (**3**_{n=6}, **3**_{n=8} and **3**_{n=10}), each component being introduced in a ratio matching the targeted ratio of the final pheromone mixture

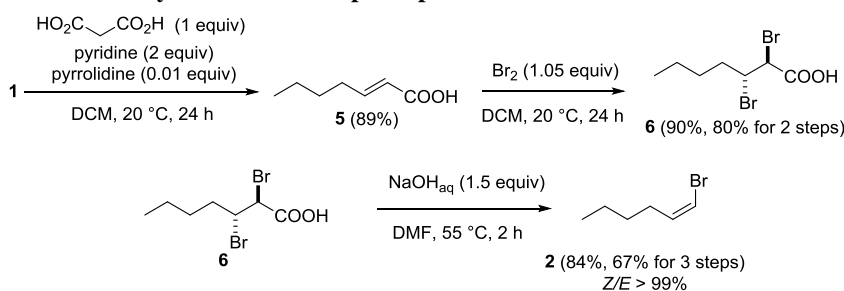
Scheme 2. Synthesis route toward pheromone of *Spodoptera frugiperda* described in this work.



((**Z7-12:Ac**)/(**Z9-14:Ac**)/(**Z11-16:Ac**) in a 2.1/78.3/19.6 ratio). This will allow the access to the final pheromone in which all components have the expected ratio in a one-pot sequence.

This method thus affords the *Spodoptera frugiperda* pheromone blend in a 7-step procedure, with 4 steps realized

Scheme 3. Synthesis of electrophilic partner **2.**



in a single-pot sequence (Scheme 2: preparation of Grignard coupling partners, Fe-mediated coupling, acylation). An overall 61% yield is obtained with respect to pentanal **1**. Moreover, this method can easily be scaled up, and 20 g of the final pheromone have been obtained with the expected composition. It is also worth mentioning that the composition of the final pheromone can easily be adjusted depending on the nature of the targeted pest, making it applicable to a broad scope of insect populations.

RESULTS AND DISCUSSION

Preparation of the C₁-C₆ synthon (2**).** 1Z-hexenyl bromide **2** was readily prepared from pentanal **1** in a 3-step procedure using 2,3-dibromoheptanoic acid **6** as a key intermediate (Scheme 3). **1** was first subjected to a Knoevenagel reaction with malonic acid leading to *trans*-hepten-2-oic acid **5** (20 °C, 24 h, 89% yield). Bromination of **5** was then performed by addition of Br₂ in DCM during 24 h at 20 °C, affording 2,3-dibromoheptanoic acid **6** (90% yield). Debromodecarboxylation of **6** was then performed in mild conditions, using aqueous NaOH in DMF at 55 °C. **2** was easily distilled from the bulk medium and obtained with an 84% yield and a Z/E > 99/1 ratio. This debromodecarboxylation method represents an appealing alternative to other reported methods, which rely on less easily scalable conditions, such as microwave irradiation.⁷ The 3-step Knoevenagel condensation / bromination / debromodecarboxylation sequence thus allows obtention of **2** from **1** in an overall 67% yield.

Preparation of nucleophilic coupling partners **4_{n=6,8,10}.** Formation of α,ω-difunctionalized Grignard reagents bearing a terminal alkoxide moiety from the corresponding chloroalcohols has already been described by Cahiez.⁸ Aiming at obtaining a final mixture of compounds (**Z7-12:Ac**)/(**Z9-14:Ac**)/(**Z11-16:Ac**) in a 2.1/78.3/19.6 ratio, formation of a mixture of coupling partners **4**_{n=6,8,10} with the same molar ratio was performed from the corresponding mixture of the α,ω-chloroalcohols **3**_{n=6,8,10} (Table 1). Treatment of the latter mixture in Cahiez conditions (action of *n*-BuMgCl in THF in the presence of Mg turnings (resp. 1.05 and 1.15 equiv with

respect to the mixture of $\mathbf{3}_{n=6,8,10}$) in THF at $-10\text{ }^{\circ}\text{C}$ followed by 2 h at $50\text{ }^{\circ}\text{C}$ and further heating at $70\text{ }^{\circ}\text{C}$ during 15 h led to a near-quantitative conversion of the starting α,ω -chloroalcohols (Entry 1). However, ca. 1.5 % of $\mathbf{3}_{n=8}$ and 0.5 % of $\mathbf{3}_{n=10}$ were still detected. Some efforts were put to ensure a better conversion of the starting compounds $\mathbf{3}_{n=6,8,10}$ in this first step, their removal at further stages of the synthesis being potentially difficult. Slightly harsher conditions (use of 1.3 equiv Mg and heating at $85\text{ }^{\circ}\text{C}$, Entry 2) led to a full conversion of $\mathbf{3}_{n=6}$ and $\mathbf{3}_{n=10}$, $\mathbf{3}_{n=8}$ being detected at a trace level (0.4 %). Importantly, no side-product was formed by reduction of a C-Cl bond at the C-H stage or by formation of C-C dimeric species by Wurtz coupling, meaning that the 2.1/78.3/19.6 ratio was conserved in the $\mathbf{4}_{n=6,8,10}$ mixture. Moreover, this optimization was originally carried out at a 20 mmol scale of the $\mathbf{3}_{n=6,8,10}$ mixture (total weight : 3.5 g). A scale-up attempt was performed on a 200 mmol scale (total weight : 35 g, Entry 3), affording a similar conversion of the $\mathbf{3}_{n=6,8,10}$ mixture, demonstrating the scalability of this step.

Having in hands optimized conditions for preparation of coupling partners, the iron-catalyzed cross-coupling step was then optimized on a model reaction.

Table 1. Optimization of the preparation of the α,ω -difunctionalized Grignard partners $\mathbf{4}_{n=6,8,10}$.

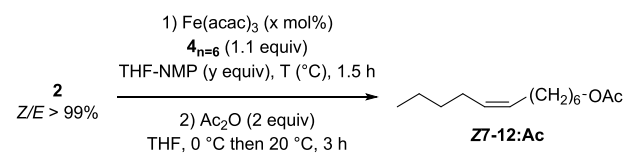
Entry	$\mathbf{3}_{n=6,8,10}$ Scale (mmol)	1) mixture $\mathbf{3}_{n=6,8,10}$ (2.1/78.3/19.6 ratio, 1 equiv)		T ($^{\circ}\text{C}$)	Conversion (%) ^a	Remaining $\mathbf{3}_{n=6,8,10}$ ^a
		BuMgCl x equiv.	Mg y equiv.			
		2) THF, T ($^{\circ}\text{C}$), 15 h				
1	20	1.05	1.15	70	> 98	$\mathbf{3}_{n=8}$ (1.5 %) $\mathbf{3}_{n=10}$ (0.5 %)
2	20	1.05	1.30	85	> 99	$\mathbf{3}_{n=8}$ (0.4 %)
3	200	1.05	1.30	85	> 99	$\mathbf{3}_{n=8}$ (0.6 %)

^a GC-MS, using *n*-decane as an internal standard.

Optimization of the cross-coupling / acylation sequence.

In order to obtain the most efficient coupling conditions, cross-coupling between $\mathbf{2}$ and $\mathbf{4}_{n=6}$ as the sole electrophilic partner was first optimized, and acylation of the alkoxide group with Ac_2O leading to $\mathbf{Z7-12:Ac}$ was subsequently performed in one-pot conditions (Table 2). Fe-mediated cross-coupling between alkyl Grignard reagents and alkenyl bromides has been efficiently developed by Cahiez in 1998 at preparative scales, using NMP (N-Methylpyrrolidone) as a co-

Table 2. Optimization of the cross-coupling / acylation sequence leading to formation of $\mathbf{Z7-12:Ac}$.



Entry	$\mathbf{4}_{n=6}$ Scale (mmol)	x	y	T ($^{\circ}\text{C}$)	Yield ^a (%, 2 steps)	% (Z)
1	10	1	9	-10	90	> 99
2	10	1	3	-10	92	> 99
3	10	1	0	-10	94	> 99
4	10	1	0	10	78	> 99
5	10	0.1	0	-10	94	> 99
6 ^b	10	0.1	0	-10	93	> 99
7 ^b	100	0.1	0	-10	90 ^c	> 99

^a GC-MS, using *n*-decane as an internal standard; ^b addition of the solution of $\text{Fe}(\text{acac})_3$ and $\mathbf{2}$ to the Grignard reagent; ^c isolated yield.

solvent of THF.⁸ More recently, Cahiez and Lefèvre demonstrated that NMP could be substituted by the use of alkoxide salts such as EtOMgBr , still ensuring near-quantitative yields.⁹ Alkoxide salts are an appealing alternative to the use of NMP, which proved to be reprotoxic in the recent past.¹⁰ This advantage can be used in the cross-coupling of α,ω -difunctionalized Grignard reagents bearing themselves a terminal alkoxide moiety, thus proceeding with no need of additional ligands or additives. Following Cahiez's cross-coupling procedure with a 10 mol% $\text{Fe}(\text{acac})_3$ catalytic load at $-10\text{ }^{\circ}\text{C}$ in a 9/1 THF/NMP mixture, a 90% yield for the cross-coupling / acylation sequence was obtained, with a $Z/E > 99/1$ ratio (Entry 1). Optimization process showed that the same outcome could be observed without NMP and at a lower 0.1 mol% catalytic load (Entry 5, 94% yield). However, operating at a higher $10\text{ }^{\circ}\text{C}$ temperature for the cross-coupling led to a decrease of the overall yield (Entry 4, 78%). In entries 1-5, the Grignard reagent $\mathbf{4}_{n=6}$ was prepared *ex situ* and then added dropwise onto a solution containing $\text{Fe}(\text{acac})_3$ and $\mathbf{2}$. Aiming at simplifying the procedure, we examined the feasibility of adding the $\text{Fe}(\text{acac})_3$ / $\mathbf{2}$ solution onto the Grignard reagent following its preparation (Entry 6). A similar 93% yield and a $> 99\%$ Z/E selectivity is obtained in these conditions, allowing to perform the Grignard synthesis / cross-coupling / acylation 4-step sequence in a single pot. GC-MS analysis of the crude mixture only evidenced impurities that are more volatile than $\mathbf{Z7-12:Ac}$, which encouraged us to operate a purification by distillation under reduced pressure (2 mbar at $100\text{ }^{\circ}\text{C}$). This was performed at a higher 100 mmol scale (Entry 7), and afforded a 90% isolated yield for $\mathbf{Z7-12:Ac}$ (20.4 g). In the last part of this report, we discuss the application of this

strategy to the obtention of the pheromone of *Spodoptera frugiperda*.

Table 3. Optimization of the cross-coupling / acylation sequence leading to pheromone of *Spodoptera frugiperda*.

Entry	2 (Scale, mmol)	x	Expected ratio Z7/Z9/Z11	Observed ratio. ^a Z7/Z9/Z11	Isolated Yield (%)
1	10	1.1	2.1/78.3/19.6	1.8/79.1/19.1	94
2	100	1.1	2.1/78.3/19.6	1.5/77.7/20.8	94

^a GC-MS, using *n*-decane as an internal standard.

Synthesis of the pheromone blend of *Spodoptera frugiperda*. In order to obtain the expected pheromone mixture ((Z7-12:Ac)/(Z9-14:Ac)/(Z11-16:Ac) in a 2.1/78.3/19.6 ratio), a mixture of the alcohols $3_{n=6,8,10}$ in the same ratio was used as a starting material and converted into the corresponding mixture of Grignard reagents $4_{n=6,8,10}$ in the conditions of Table 1, Entry 2. This mixture was treated in the cross-coupling / acylation conditions developed in Table 2. The expected pheromone mixture is obtained with a 94% yield, and a 1.8/79.1/19.1 ratio, close to the expected 2.1/78.3/19.6 value, each component displaying a *Z/E* > 99/1 ratio (Table 3, Entry 1). Purification of the final product is performed by distillation under reduced pressure in slightly harsher conditions (110 °C, 2 mbar) in order to remove traces of compound Cl-(CH₂)₈-OAc, formed by acylation of $3_{n=8}$, which was not fully converted into Grignard reagent $4_{n=8}$ (Table 1, Entry 3). A scale-up was then performed on a 100 mmol scale (Entry 2), leading to similar results. However, a slight loss of the less heavy of the pheromone components (Z7-12:Ac) is observed (the latter representing 1.9 mol% of the mixture distribution before distillation, and 1.5 mol% after), due to a harsher distillation process required to fully remove Cl-(CH₂)₈-OAc (115 °C, 2 mbar at a 100 mmol scale).

In summary, we have reported a convenient synthesis of the *Spodoptera frugiperda* pheromone blend, which enables a direct access to the expected 3-component mixture with a

controlled ratio for each of the components. This method displays an overall 61% yield with respect to *n*-pentanal, used to prepared the electrophilic synthon of a key iron-mediated cross-coupling. The absence of any ligand for the latter step as well as the possibility to carry out a 4-step sequence in a single pot make this method particularly attractive for high-scale synthesis. As a proof of concept of this scalability, an analytically pure 20 g batch of the final mixture has been prepared. This method improves the current state of the art for the synthesis of this target, as it allows a direct joint preparation of the three components of the pheromone in a controlled ratio, sparing the need to separately prepare each of the blend constituents.

EXPERIMENTAL SECTION

Gas chromatography analyses (GC) and mass spectra were performed on a Hewlett-Packart HP 5973 mass spectrometer via a GC/MS coupling with a Hewlett-Packart HP 6890 chromatograph equipped with a capillary column HP-5MS (50 m x 0.25 mm x 0.25 μm, 5% polysilarylene / 95% polydimethylsiloxane). Ionisation was performed by electronic impact (EI, 70 eV). Mass spectra are reported as *m/z* (molecular ion peak, % of relative intensity). Helium was used as a carrier gas (1.0 mL/min, ratio split: 100). Standard analysis conditions: 40°C (hold 1 min) to 250°C (hold 10 min), heating rate: 20°C/min. Standard flash column chromatography was performed on silica gel 60. ¹H NMR (400 MHz, CDCl₃), ¹³C NMR (100 MHz, CDCl₃) were recorded on a Bruker Avance III HD 400 instrument. Chemical shifts (δ) are given in ppm from TMS (¹H, ¹³C). Coupling constants (*J*) are given in Hz. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). All reagents and solvents were obtained from either Sigma-Aldrich, Acros, Alfa, VWR, or TCI and were used as received unless otherwise stated. High purity Fe(acac)₃ (>99%) from Sigma-Aldrich was used. Dry solvents were obtained from commercial sources. All reactions were conducted in dry flasks under argon atmosphere. Titration of Grignard reagents was performed according to the procedure reported by Watson¹⁹ by using a 1 M solution of sec-butyl alcohol in toluene, 1 mL of the THF solution of the Grignard reagent, and 1–2 mg of 2,2-biquinoline.

trans-hepten-2-oic acid (5). In a dry four-neck 2 L round-bottom flask equipped with a mechanical stirrer, a thermometer, a condenser and an argon inlet were introduced, at 20 °C, malonic acid (100 g, 1.0 mol, 1.0 equiv), pyridine (155 mL, 2.0 mol, 2 éq.), pyrrolidine (0.83 mL, 0.01 mol, 0.01 equiv) and dichloromethane (500 mL). The mixture was stirred around 30 min until total dissolution of the reactants. Pentanal (86 g, 1.0 mol, 1.0 equiv) was then added slowly to limit the elevation of temperature. The mixture was stirred 24 h at 20 °C until total consumption of malonic acid and finally quenched at 0 °C by adding dropwise 500 mL of an aqueous solution of HCl (5 M). After verifying that pH = 1, the aqueous layer was extracted with 3 x 250 mL of methyl *tert*-butyl ether (MTBE). The combined organic layers were washed with 600 mL of a saturated NaCl aqueous solution and concentrated under vacuum at 40°C. The resulting crude was dissolved in 200 mL of MTBE and concentrated under vacuum again to afford 114 g (89%) of an transparent oil. ¹H-NMR (CDCl₃, 400 MHz) δ 7.10 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.83 (dt, *J* = 15.6, 1.5 Hz, 1H), 2.28-2.22 (m, 2H), 1.51-1.31 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H). ¹³C-NMR (CDCl₃, 100 MHz) δ 172.1, 152.7, 120.4, 32.2, 30.1, 22.4, 14.0.

2,3-dibromoheptanoic acid (6). In a dry four-neck 2 L round-bottom flask equipped with a mechanical stirrer, a thermometer, a

condenser and an argon inlet were introduced, at 20 °C, *trans*-hept-2-enoic acid (115 g, 0.9 mol, 1.0 equiv) and dichloromethane (400 mL). At 0 °C, a solution of dibromide (151 g, 0.95 mol, 1.05 equiv) in dichloromethane (100 mL) was progressively added to the mixture to remain under 5 °C. After the addition, the resulting mixture was stirred overnight at 20 °C and then quenched by 400 mL of a half-saturated aqueous solution of Na₂S₂O₅. The aqueous layer was extracted with 3 x 100 mL of DCM and the combined organic layers were washed with saturated aqueous NaCl solution, dried over magnesium sulfate, filtered, and concentrated under vacuum at 40 °C. 230 g (90%) of a yellow solid was obtained and was used in the next step without purification. ¹H-NMR (CDCl₃, 400 MHz) δ 4.45 (d, *J* = 11.1 Hz, 1H), 4.39-4.34 (m, 1H), 2.30-2.22 (m, 1H), 1.91-1.79 (m, 1H), 1.62-1.32 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 3H). ¹³C-NMR (CDCl₃, 100 MHz) δ 173.6, 52.0, 47.5, 34.8, 28.4, 22.0, 14.0.

Z-bromohex-1-ene (2). In a dry four-neck 2 L round-bottom flask equipped with a mechanical stirrer, a thermometer, a condenser and an argon inlet were introduced, at 20 °C, 2,3-dibromoheptanoic acid (35.3 g, 120 mmol, 1.0 equiv) and dimethylsulfoxide (80 mL). The mixture was heated up to 50 °C then a 33% w/w aqueous solution of NaOH (192 mmol, 1.6 equiv) was slowly added. After the addition, the mixture was heated up to 100 °C to perform the distillation of the product. The resulting distillate was washed two times with water and stored on molecular sieve 4 Å and 1.6 g (84%) of a colorless liquid was finally obtained. ¹H-NMR (CDCl₃, 400 MHz) δ 6.16-6.07 (m, 2H), 2.24-2.17 (m, 2H), 1.41-1.34 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ 135.0, 107.5, 30.3, 29.4, 22.2, 13.9.

General procedure for the optimization of ClMg-(CH₂)_n-OMgCl (4_{n=6,8,10}) formation. Into a dry four-neck 100 mL round-bottom flask equipped with magnetic stirring, a condenser, a thermometer, and an argon inlet were introduced magnesium (*x* + *y* equiv) and THF (4 mL). Ethyl bromide (30 μL, 0.4 mmol, 0.04 equiv) was added instantaneously under vigorous stirring, and the reaction mixture was then stirred at 40 °C. A solution of *n*-butyl chloride (*x* equiv) in THF (20 mL) was added dropwise in 1 h, and after the end of the addition, the mixture was stirred for 3 h at 50 °C. The reaction mixture was cooled to -10 °C, and 6-chlorohexan-1-ol (3_{n=6}, 59 μL, 0.42 mmol, 0.021 equiv), 8-chlorooctan-1-ol (3_{n=8}, 2.781 mL, 15.66 mmol, 0.783 equiv) and 10-chlorodecan-1-ol (3_{n=10}, 802 μL, 3.92 mmol, 0.196 equiv) were added dropwise in 45 min (*T* < 0 °C). The cooling bath was removed, and the reaction mixture was stirred for 1 h at 50 °C and then overnight under reflux. After cooling to room temperature, the expected mixture of Grignard reagent ClOMg(CH₂)_nMgCl was obtained as a THF solution which was titrated.

General procedure for the optimization of (Z)-bromohex-1-ene (2) coupling with 3_{n=6} followed by acylation (formation of Z7-12:Ac). Into a dry 100 mL Young round-bottom flask equipped with magnetic stirring and an argon inlet were introduced (Z)-1-bromohexene (1.763 mL, 10 mmol, 1 equiv), Fe(acac)₃ (*x* mol%), NMP (*y* equiv) and THF (10 mL). The reaction mixture was cooled to -10 °C in an ice bath and ClMgO(CH₂)₆MgCl (11 mmol, 1.1 equiv) was added dropwise over 45 min under stirring (*T* < 0 °C). After total consumption of (Z)-1-bromohexene observed by GC, acetic anhydride (1.910 mL, 20 mmol, 2 equiv) was added dropwise in 10 min at 5 °C. After stirring the reaction mixture for 3 h at 20 °C, it was quenched by addition of 50 mL of a saturated aqueous solution of NH₄Cl. After decantation, the aqueous layer was extracted with MTBE (3 x 20 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over magnesium sulfate, filtered, and concentrated under vacuum. GC yield was measured

via GC-MS by adding decane as internal standard. GC: *t*_R = 8.945 min. ¹H-NMR (CDCl₃, 400 MHz) δ 5.35-5.30 (m, 2H), 4.04 (t, *J* = 6.8 Hz, 2H), 2.04 (s, 3H), 2.05-1.97 (m, 4H), 1.65-1.58 (m, 2H), 1.32-1.29 (m, 10H), 0.88 (m, 3H). ¹³C-NMR (CDCl₃, 100 MHz) δ 171.2, 130.0 (2C), 64.6, 31.9, 29.6, 28.9, 28.6, 27.0, 26.9, 25.8, 22.3, 21.0, 14.0. Same strategy was applied to obtain pure standards of Z9-14:Ac and Z11-16:Ac whose characterizations are given thereafter.

Z9-14:Ac. ¹H-NMR (CDCl₃, 400 MHz) δ 5.35-5.33 (m, 2H), 4.04 (t, *J* = 6.8 Hz, 2H), 2.02 (s, 3H), 2.03-1.99 (m, 4H), 1.63-1.59 (m, 2H), 1.33-1.29 (m, 14H), 0.90 (m, 3H). ¹³C-NMR (CDCl₃, 100 MHz) δ 171.2, 130.0 (2C), 64.7, 32.0, 29.8, 29.4, 29.2 (2C), 28.6, 27.2, 26.9, 25.9, 22.4, 21.0, 14.0.

Z11-16:Ac. ¹H-NMR (CDCl₃, 400 MHz) δ 5.34-5.32 (m, 2H), 4.05 (t, *J* = 6.8 Hz, 2H), 2.04 (s, 3H), 2.05-2.00 (m, 4H), 1.65-1.56 (m, 2H), 1.33-1.29 (m, 18H), 0.88 (m, 3H). ¹³C-NMR (CDCl₃, 100 MHz) δ 171.2, 130.0 (2C), 64.6, 32.0, 29.7, 29.5 (3C), 29.2, 29.2, 28.6, 27.2, 26.9, 25.9, 22.3, 21.0, 14.0.

Synthesis of *Spodoptera frugiperda* pheromone blend. Into a dry four-neck 500 mL round-bottom flask equipped with magnetic stirring, a condenser, a thermometer, and an argon inlet was prepared a ClMg-(CH₂)_n-OMgCl mixture in optimized conditions starting from a total of 100 mmol of Cl-(CH₂)_n-OH. 80 mL of THF were added to dilute the reaction mixture which was then cooled to -10 °C in an ice bath. Fe(acac)₃ (35.3 mg, 0.1 mmol, 0.1 mol%) was added in one portion to the mixture then (Z)-1-bromohexene (17.628 g, 100 mmol, 1.0 equiv) was added dropwise over 45 min (*T* < 0 °C). After total consumption of (Z)-1-bromohexene observed by GC, acetic anhydride (19.097 mL, 200 mmol, 2 equiv) was added dropwise in 15 min at 0 °C. After stirring the reaction mixture for 3 h at 20 °C, it was quenched by addition of 200 mL of a saturated aqueous solution of NH₄Cl. After decantation, the aqueous layer was extracted with MTBE (3 x 50 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (200 mL), dried over magnesium sulfate, filtered, and concentrated under vacuum. The resulting crude was finally distilled under reduced pressure to eliminate volatile impurities. Composition of the final mixture was assessed on the basis of GC-MS analysis by comparison with pure standards of Z7-12:Ac, Z9-14:Ac and Z11-16:Ac.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. The SI PDF file contents ¹H and ¹³C NMR spectra of compounds discussed in this work.

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Direct access to 3-component pheromonal blend

