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EFFICIENT SYNTHESIS OF (5*Z*,7*E*)-DODECADIENAL, THE SEX PHEROMONE OF THE EUROPEAN PINE MOTH *Dendrolimus pini*

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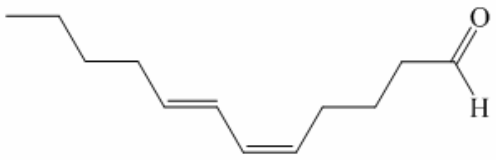
Efficient synthesis of (5*Z*,7*E*)-dodecadienal, the sex pheromone of European pine moth *Dendrolimus pini*, was stereoselectively accomplished via Pd- and Fe- catalyzed cross-coupling reactions in the key steps. The very simple and practical method developed herein provides a general synthetic approach to other (*Z*,*E*)-diene compounds.



INTRODUCTION

The pine tree lappet moth caterpillars *Dendrolimus pini* is a serious defoliator of the pine trees in Europe and Northern Asia and its population often fluctuates between endemic and epidemic levels.[1] As a consequence, many trees die during severe outbreaks, because the defoliated trees become susceptible to diseases, bark beetles and wood boring insects.

Mating disruption (MD) is an insect pest management technique designed to control insect pests by introducing artificial stimuli that confuse the individuals and disrupt mate localization and/or courtship, thus preventing mating and blocking the reproductive cycle. The MD technique involves the use of synthetic sex pheromones as a volatile organic chemical to mimic the species-specific sex pheromone produced by the female insect.

In this context, we were interested to develop a new mating disruption (MD) system to control the populations of *Dendrolimus pini* using the synthetic pheromone (5*Z*,7*E*)-dodecadienal **1**. The pheromone (5*Z*,7*E*)-dodecadienal has been identified in female pheromone gland extracts of *D. pini* by Priesner *et al.*[2] and many synthetic procedures for the synthesis of **1** have been reported.[3-8] Chisholm *et al.*[4] have synthesized all four geometrical isomers of (5,7)-dodecadien-1-ol **7** using Wittig condensation reactions. The mixed geometrical isomers of the conjugated dienyl alcohols were resolved by elution with methanol from a silver cation resin at 20 ºC, which is a difficult procedure for a scale-up synthesis. Ando *et al.*[6] reported a new method for the synthesis of (5*Z*,7*E*)-dodecadien-1-ol **7** using hydrozirconation, coupling reactions by palladium catalysts and selective hydrogenations. The Lindlar reduction of (*E*)-7-dodecen-5-yn-1-ol lacked selectivity, providing a mixture of (*Z,E*)-diene and monoenic compounds. The desired product was isolated by chromatography on silica impregnated with silver nitrate. Khrimian *et al.*[7] applied an activated zinc hydrogenation technique to synthesize (5*Z*,7*E*)-dodecadien-1-ol **7** from (*E*)-7-dodecen-5-yn-1-ol. Zinc activated with copper and silver has been used in the *cis* reduction. Grodner and Zander[8]

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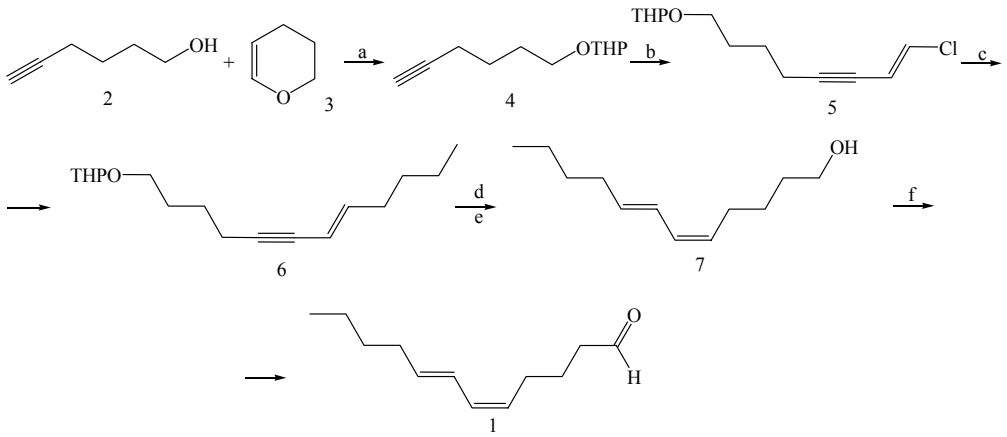
reported also the synthesis of (5*Z*,7*E*)-dodecadienal **1** in seven steps from the commercially available 5-hexyn-1-ol **2**, (5*Z*,7*E*)-1,1-diethoxy-5,7-dodecadiene being the immediate precursor for the pheromone **1**. All of the described methods use intermediates in the coupling reactions, which are difficult to synthesize often using more than six reaction steps.

RESULTS AND DISCUSSION

Herein we report a new stereoselective approach for the synthesis of pheromone **1** from cheap and readily available starting materials, using Pd and Fe catalyzed cross-coupling reactions for the construction of the entire skeleton of **1** (Scheme 1). The synthesis of (5*Z*,7*E*)-Dodecadienal **1** starts with the protection of 5-hexyn-1-ol **2** with 3,4-dihydro-2*H* pyran **3** to give 1-(tetrahydropyran-2-yloxy)-5-hexyne **4** in 94% yield after purification.[9] The stereospecific introduction of the double bond, for the construction of the enyne moiety, was achieved by the Pd(0)-catalyzed cross-coupling reaction between terminal alkynes and haloalkenes.[10,11]

Thus, the cross-coupling reaction of alkyne **4** with 1,2-(*E*)-dichloroethylene in the presence of 5 mol% $PdCl_2(PPh_3)_2$, 10 mol% CuI and piperidine afforded the (*E*)-chloroenyne derivative **5** in very good yield (84%) and high isomeric purity (> 99% by GC). The *E*-configuration of chloroenyne **5** was confirmed by ^{1}H NMR spectra which showed a doublet at 6.43 ppm with J_{trans} = 13.6 Hz and a multiplet at 5.96-5.84 ppm, respectively. The iron-catalyzed alkenylation of organomagnesium compounds[12-13] was used for the construction of the entire carbon chain of the pheromone **1**. Reaction of *n*-butylmagnesiumbromide with (*E*)-chloroenyne **5** in the presence of 3 mol % $FeCl_3$ in THF-DMPU (1,3-dimethyl-3,4,5,6-tetrahydro2(1*H*)-pyrimidinone) as solvent, afforded (*E*)-1-(tetrahydropyran-2-yloxy)-dodec-7-en-5-yne **6** in good yield (75%) with full retention of the configuration of the double bond proved by GC-MS analysis (> 99%). The *E*-configuration of butylenyne **6** was again confirmed by ^{1}H NMR spectra, which showed a doublet of triplets at 6.04 ppm (J_{trans} = 15.8 Hz and J = 7.1 Hz) and a doublet of quintets at 5.44 ppm (J_{trans} = 15.8 Hz and J = 1.9 Hz), respectively. The stereoselective hydroboration[14] of the triple bond in butylenyne **6** with dicyclohexylborane and subsequent protonolysis of the vinyl-boron intermediate with acetic acid gave the desired (*E*,*Z*)-diene, which was directly converted into the corresponding alcohol **7** after deprotection in MeOH in the presence of catalytic amount of *p*-TsOH.[6, 15] The yield for both steps was 55%. The (*E*, *Z*) configuration of **7** was confirmed by ^{1}H NMR spectra which showed a triplet at 5.96 ppm J_{cis} = 10.9 Hz for the *Z*-configured double bond and a doublet of triplets at 5.66 ppm J_{trans} = 14.6 Hz and J = 7.0 Hz for the *E*-configured double bond, respectively. (5*Z*,7*E*)-Dodecadien-1-ol **7** was oxidized with pyridinium chlorochromate in the presence of sodium acetate[16] to provide the desired pheromone (5*Z*,7*E*)-dodecadien-1-al **1** in good yield (64%) and stereoisomeric purity (98% from GC-MS analysis). The overall yield of the target compound was 44%. The ^{1}H NMR, ^{13}C NMR, and GC-MS (Fig. 1) data of compound **1** were in excellent agreement with those reported previously.[3, 6-8]



a. PPTS, CH_2Cl_2, r.t.; b. 1,2(*E*)-dichloroethylene, $Pd(PPh_3)_2Cl_2$, CuI, piperidine, THF, r.t.;
c. BuMgBr, $FeCl_3$, DMPU, THF r.t.; d. Cy_2BH, THF, 0°C→r.t., CH_3COOH, 0°C→r.t.; e. *p*-TsOH, MeOH, r.t.; f. PCC, CH_2Cl_2, r.t.

Scheme 1 – Synthesis of pheromone **1**.

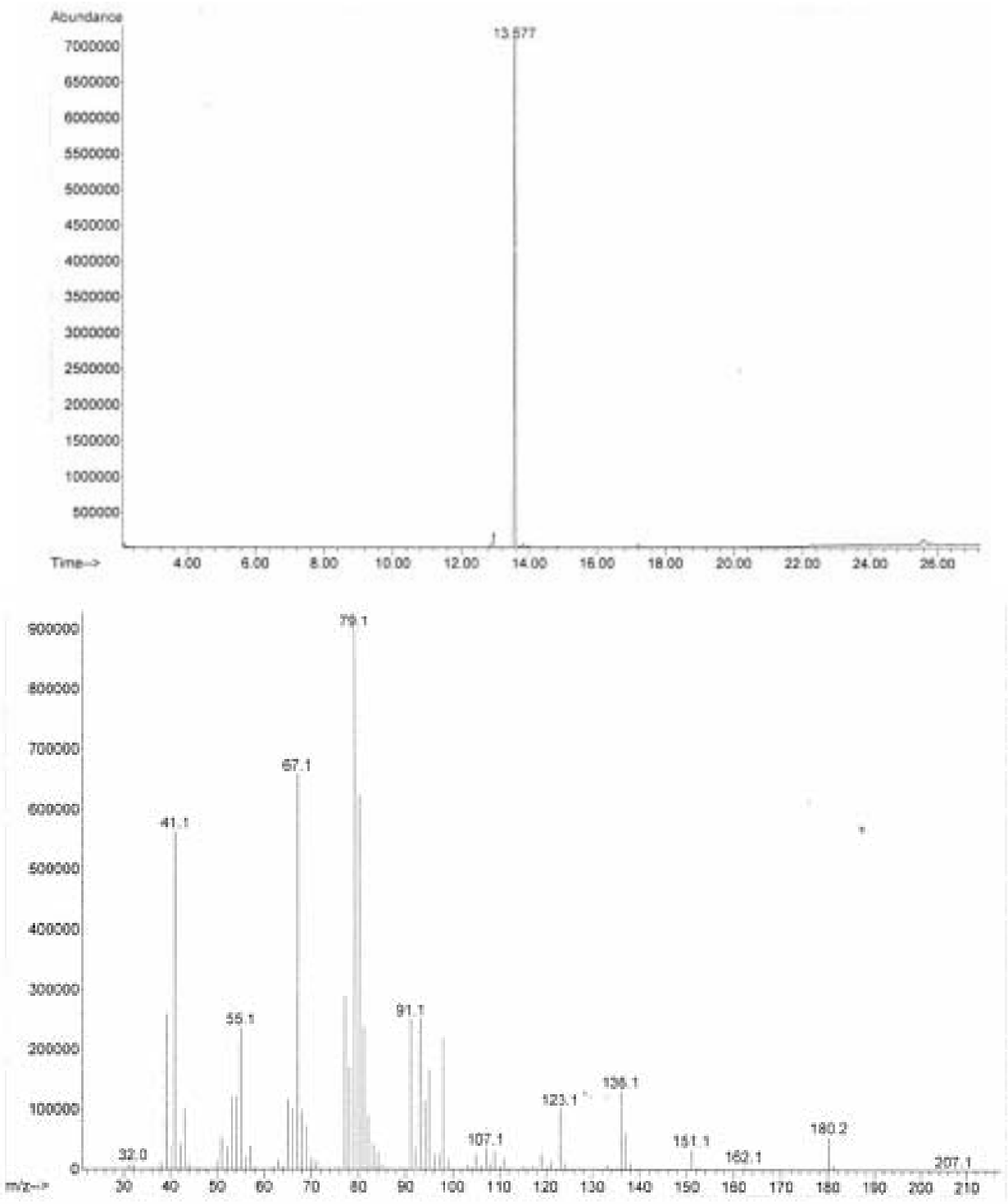


Fig. 1 – GC chromatogram and MS-EI spectrum of synthesized pheromone **1**.

The synthetic pheromone **1** was formulated on a granulate in order to develop a new mating disruption (MD) system that interferes with the male's ability to find a female, resulting in reduced mating and egg laying by females. The new product is under tests in Germany, by Flügel GmbH, and the results will be published in another paper.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker Biospin 600 MHz spectrometer in $CDCl_3$, using the residual solvent peak as internal reference. EI-MS (70 eV) mass spectra were recorded on Hewlett-Packard 5972 GC-MS instrument and on Agilent Technologies 7890A/5875A GC-MS system.

Commercially available chemicals and reagents were purchased from common chemical suppliers and used without purification. All solvents were dried and purified according to standard procedures. All air-sensitive reactions were carried out in inert atmosphere under argon. Pd catalyst was prepared as described in the literature.[17] GC column (phenylmethylsiloxane) HP-5MS (30 m x 0.25 mm x 0.25 μm) was used. Preparative column chromatography was performed on silica gel (Merck, Darmstadt) mesh 70-230. Thin layer chromatography (TLC) was performed on silica gel layered aluminum foil (60 F_{254} Merck, Darmstadt).

(*E*)-8-(Tetrahydropyran-2-yloxy)-1-chloroocta-1-en-3-yne 5. A mixture of 5-hexyne-1-ol (9.3 g, 94.9 mmol), 3,4-dihydro-2*H* pyran (9.56 g, 113.8 mmol) and pyridinium p-toluenesulfonate (PPTS) (2.56 g, 10.2 mmol) in 280 mL CH_2Cl_2 was stirred at r.t. until the disappearance of the starting materials. The solution was concentrated under vacuum and the crude product was purified by column chromatography using *n*-hexane/diethyl ether, 10:1 as eluent, to give the protected alcohol **4** (16.3 g, 89.56 mmol, 94%).

A mixture of $PdCl_2(PPh_3)_2$ (5 mol%, 4.47 mmol, 3.13 g), (*E*)-1,2-dichloroethene (358 mmol, 34.72 g), 1-(tetrahydropyran-2-yloxy)-5-hexyne **4** (89.5 mmol, 16.3 g) and piperidine (268.5 mmol, 22.82 g) in anhydrous THF (750 mL) was stirred for 15 min at room temperature under argon atmosphere, then CuI (10 mol%, 8.95 mmol, 1.7 g) was added. The stirring was continued until TLC analysis indicated complete consumption of the alkyne. The reaction mixture was filtered and the solvent was removed in vacuum. The residue was dissolved in diethyl ether (500 mL) and treated with saturated aqueous solution of $NaHCO_3$, then with brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed in vacuum. The crude product was purified by column chromatography (*n*-hexane/diethyl ether, 10/1) to yield the desired (*E*)-chloroenyne **5** (75.46 mmol, 18.30 g, 84%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.43 (d, *J* = 13.6 Hz, 1H), 5.96-5.84 (m, 1H), 4.58-4.57 (m, 1H), 3.88-3.84 (m, 1H), 3.77-3.74 (m, 1H), 3.53-3.47 (m, 1H), 3.40 (dt, *J* = 9.7, 6.2 Hz, 1H), 2.34 (td, *J* = 7.0, 2.2 Hz, 2H), 1.85-1.78 (m, 1H), 1.75-1.66 (overlapped signals, 3H), 1.65-1.60 (overlapped signals, 2H), 1.59-1.48 (m, 4 H); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 128.97, 114.39, 99.02, 93.21, 76.05, 67.07, 62.51, 30.90, 29.09, 25.64, 25.50, 19.80, 19.41; GC: t_r = 18.71; isomeric purity: 99%; MS(EI) (*m/z*): 207 (5%), 189 (1%), 158 (2%), 123 (2%), 105 (14%), 85 (100%), 57 (10%), 41 (16%).

(*E*)-1-(Tetrahydropyran-2-yloxy)-dodec-7-en-5-yne 6. To a solution of **5** (78.35 mmol, 16.0 g) and $FeCl_3$ (3 mol%, 2.35 mmol, 0.38 g) in a mixture of THF (80 mL) and DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) (65 mL) was added dropwise (over 20 min) a solution of butylmagnesium bromide (prepared from *n*-butylbromide (313.4 mmol, 42.93 g) and Mg (344.74 mmol, 8.27 g) in 290 mL THF at room temperature). Stirring was continued until all starting materials have been consumed. The reaction mixture was hydrolyzed at 0 ºC with aqueous 1 M HCl. After separation of the phases, the aqueous layer was extracted with Et_2O (2 x 200 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum and the crude product was purified by column chromatography (petroleum ether/diethyl ether, 10/1), to yield the desired enyne (**6**) (49.62 mmol, 13.1 g, 75%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.04 (dt, *J* = 15.8, 7.1 Hz, 1H), 5.44 (qt, *J* = 15.8, 1.9 Hz, 1H), 3.87-3.84 (m, 1H), 3.75 (dt, *J* = 9.7, 6.5 Hz, 1H), 3.54-3.46 (m, 1H), 3.40 (dt, *J* = 9.7, 6.5 Hz, 1H), 2.32 (td, *J* = 7.1, 2.1 Hz, 2 H), 2.07 (qd, *J* = 7.1, 1.5 Hz, 2 H), 1.88-1.78 (m, 1 H), 1.75-1.66 (overlapped signals, 3 H), 1.64-1.48 (overlapped signals, 7 H), 1.40-1.25 (overlapped signals, 4 H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 143.58, 109.88, 98.94, 88.40, 79.59, 67.16, 62.43, 32.77, 31.10, 30.89, 29.12, 25.80, 25.64, 22.28, 19.77, 19.35, 13.99; GC: t_r = 21.68, isomeric purity 99%; MS(EI) (*m/z*): 264 (0.3%), 221 (2%), 207 (8%), 193 (7%), 179 (3%), 149 (2%), 137 (6%), 121 (3%), 105 (5%), 85 (100%), 67 (20%), 55 (14%), 41 (21%).

(5*Z*,7*E*)-Dodecadien-1-ol 7. A solution of cyclohexene (114 mmol, 9.35 g) in THF (30 mL) was added dropwise to a solution of BH_3-dimethylsulfide complex (57.04 mmol, 4.34 g) in THF (50 mL) at 0 ºC under argon. The reaction mixture was stirred for 2 h at –10 - 0 ºC, then allowed to warm up to room temperature and stirred for 1.5 h. The resulting white slurry of dicyclohexylborane was cooled back to 0 ºC and a solution of (**6**) (49.6 mmol, 13.1 g) in 20 mL THF was added dropwise over 20 min. The resulting mixture was stirred for 2 h at 0 ºC and then allowed to warm up to room temperature and stirred overnight. The reaction mixture was cooled to 0 ºC, glacial acetic acid (30 mL) was added and the mixture was warmed to room temperature and stirred overnight. The solution was diluted with Et_2O (300 mL), washed with water, saturated aqueous solution of $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum and the resulting residue was purified by flash chromatography (petroleum ether/diethyl ether, 40/1), to yield the crude diene (33.0 mmol, 8.8g, 67%). GC-MS analysis: t_r = 20.78 min, chemical purity 88%, isomeric purity 99%); MS(EI) (*m/z*): 266 (0.5%), 182 (1 %), 164 (1%), 136 (1%), 121 (1%), 109 (2%), 85 (100%), 67 (23%), 55 (13%), 41 (20%).

p-Toluenesulfonic acid (2.5 mmol, 0.5 g) was added to a solution of crude diene (25.00 mmol, 6.7 g) in methanol (500 mL). The mixture was stirred at room temperature overnight and then concentrated in vacuum. The residue was diluted with diethyl ether (200 mL), washed with saturated aqueous solution of $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum and the crude product was purified by column chromatography (ethyl acetate/*n*-hexane, 1/3) to yield the desired alcohol (**7**) (22.36 mmol, 4.07 g, 89%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.36-6.20 (m, 1H), 5.96 (t, *J* = 10.9 Hz, 1H), 5.66 (dt, *J* = 14.6 Hz, 7.0 Hz, 1H), 5.33-5.22 (m, 1H), 3.65 (t, *J* = 6.6 Hz, 2H), 2.20 (qd, *J* = 7.5, 1.2 Hz, 2H), 2.09 (q, *J* = 7.0 Hz, 2H), 1.63-1.55 (m, 2H), 1.49-1.42 (m, 2H), 1.40-1.28 (m, 5H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 135.17, 129.47, 129.20, 125.60, 63.02, 32.70, 32.47, 31.69, 27.51, 25.99, 22.42, 14.08; GC: t_r = 14.73, chemical purity 93%, isomeric purity 99%; MS(EI) (*m/z*): 182 (6%), 164 (9%), 135 (5%), 121 (12%), 107 (11%), 93 (33%), 79 (97%), 67 (100%), 55 (49%), 41 (66%), 31 (24%).

(5*Z*,7*E*)-Dodecadien-1-al 1. (5*Z*,7*E*)-Dodecadien-1-ol **7** (22.36 mmol, 4.07 g) was oxidized with pyridinium chlorochromate (26.83 mmol, 5.78 g) in dry methylene chloride (350 mL) at room temperature for 4 hours to provide **1** (14.27 mmol, 2.57 g, 64%) after purification on column chromatography (*n*-hexane/diethyl ether, 10/1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.78 (t, *J* = 1.6 Hz, 1H), 6.25 (ddq, *J* = 14.9, 10.5, 1.4 Hz, 1H), 6.00 (dd, *J* = 11.3, 10.5, 1H), 5.69 (dt, *J* = 14.9, 7.0 Hz, 1H), 5.24 (dt, *J* =11.3, 7.6 Hz, 1H), 2.45

(td, J = 7.3, 1.7 Hz, 2H), 2.21 (qd, J = 7.5, 1.5 Hz, 2H), 2.10 (qd, J = 7.1, 1.4 Hz, 2H), 1.73 (p, J = 7.3 Hz, 2H), 1.38-1.29 (overlapped signals, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 202.67, 135.80, 130.12, 128.35, 125.19, 43.36, 32.70, 31.65, 27.03, 22.42, 22.20, 14.08; GC: t_r = 13.57, chemical purity 93%, isomeric purity 99%; MS(EI) (*m/z*): 180 (6%), 162 (1%), 151 (4%), 136 (14%), 123 (11%), 107 (4%), 91 (27%), 79 (100%), 67 (71%), 55 (25%), 41 (61%).

CONCLUSIONS

In conclusion, an improved, convenient synthesis accomplished via palladium and iron catalyzed cross-coupling reactions is reported. Starting from cheap and readily available raw materials and using very convenient reactions, the described method can be applied to synthesize the pheromone **1** in a large scale. The overall yield of 44% and the high stereoisomeric purity represent a significant improvement in comparison to other approaches. The results on formulation and mating disruption with the synthetic pheromone could be used to decrease the population of *Dendrolimus pini* without the use of chemical insecticides during outbreak periods.

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