Improved Practical Synthesis of the Sex Pheromone of Female Sweet Potato Weevil, *Cylas Formicarius*

Jui-Chang Tseng[*], Ming-Yuan Wu, and Wei-Lun Huang

Department of Applied Chemistry, Chaoyang University of Technology, 168, Jifeng East Rd., Wufeng District, Taichung, Taiwan, R.O.C.

Abstract: An improved synthesis of (*Z*)-dodec-3-en-1-yl (*E*)-2-butenoate (**1**), the female sex pheromone of sweet potato weevil, *Cylas Formicarius*, was reported. The synthesis bypassed the utilization of carcinogenic ethylene oxide, highly toxic HMPA, highly hydroscopic and unrecyclable DMPU, ethylene diamine, and liquid ammonia, for the alkylation of terminal alkyne. Instead, NaI was used to serve as a good nucleophile for alkyl bromide and a good leaving group for 1-lithiated alkyne. A safer and stereoselective palladium-catalyzed transfer semihydrogenation, using KOH/DMF as the hydrogen source, was employed for alkyne *cis*-hydrogenation, without using molecular hydrogen. The total yield was 62% over 5 steps, and the sex pheromone **1** obtained was verified spectroscopically. Field test results showed that the synthetic sex pheromone **1** was as effective as the commercial source or the sample provided by other research group.

Keywords: *Cylas formicarius*; sweet potato weevil; sex pheromone; semihydrogenation.

1. Introduction

Sweet potato, as one of the seven most important food crops in the world, possesses remarkable importance in economic value production, energy production, and the utilization as food, feed, and industrial products [1]. It is recognized as an important health food due to rich nutrient content and good source of vitamins and minerals. Base on the released documentation from FAOSTAT in 2006 [2], sweet potatoes are grown in more than 100 countries, mainly in tropical and subtropical regions, and on about 9 million hectares (ha), producing ca. 124 million tons with an average yield of 13.7 ton/ha. In Taiwan, sweet potatoes were grown on about 9 thousand hectares, yielding 205.9 thousand tons with an average yield of 22.7 ton/ha in 2011 [3].

However, the worldwide production of sweet potatoes is severely constrained by insect feeding losses during the production and storage processes, especially by the sweet potato weevils, *Cylas formicarius formicarius* (Fabricius) and *C. formicarius elegantulus* (Summers).

After insect feeding by sweet potato weevils, an extremely bitter taste thus induced render the sweet potatoes unsuitable for further consumption, and the yield losses caused by sweet potato weevil damage range from 5% to 80% [4-6]. In addition, sweet potato weevils are difficult to control with conventional pesticides due to their cryptic nature and increasingly pesticide resistance. Nevertheless, in order to reduce the pest populations without utilizing toxic pesticides, the biological control using insect sex pheromone Is now being a highly effective method.

The sex pheromone, (*Z*)-dodec-3-en-1-yl (*E*)-2-butenoate (**1**), of female *C. formicarius*

elegantulus was first identified and synthesized by Heath et al. in 1986 [7], and the same compound was also proved to be an active attractant for male *C. formicarius formicarius* by Talekar et al. in 1989 [8]. The syntheses of the sex pheromone **1** were reported by several groups [5, 7, 9-12], and their synthetic methodologies were summarized in Scheme 1. Among these synthetic strategies, the key step is the implantation of alkene moiety either by the successive alkylation of the appropriate terminal alkyne and the *cis*-hydrogenation with molecular hydrogen in the presence of Lindlar's catalyst [5, 7, 9-12], or by the *cis*-selective Wittig olefination [13].
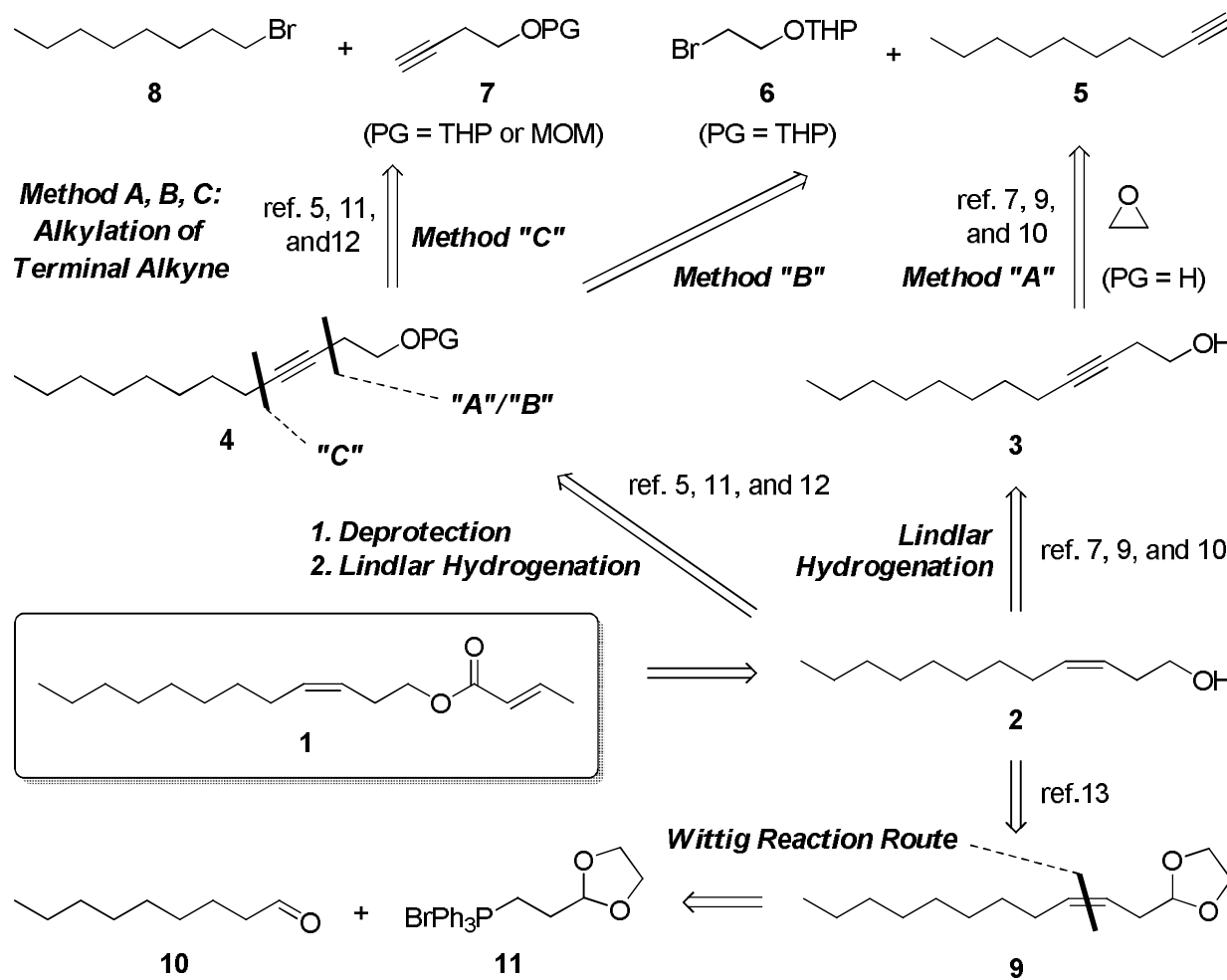

Scheme 1. Literature reported synthetic methodologies of (*Z*)-dodec-3-en-1-yl (*E*)-2-butenoate (**1**)

The synthetic strategy of alkylation Method A and C, as illustrated in Scheme 1, required the utilization of hexamethylphosphoramide (HMPA) [7, 12] or *N, N'*-dimethylpropylene urea (DMPU) [5, 9], serving as a cation solvating agent, and ethylene oxide as a ethoxyethyl chain equivalent for Method A. However, both ethylene oxide and HMPA were considered to be carcinogenic chemicals, and should be replaced with safer substitutes in large-scale synthesis. Although DMPU seemed to be a good substitute for HMPA, the reactions were usually employed stoichiometric or excess amount of DMPU (or HMPA), and the cost for the synthesis will be considerable. Moreover, HMPA and DMPU are highly hydroscopic aprotic solvents, and

required a prior freshly distilled treatment or moisture free storage. Instead of the utilization of unrecyclable HMPA or DMPU, sodium amide in liquid ammonia [11] or ethylene diamine [10] can be used as alternatives, however, the cost for practical synthesis remained as an issue. On the other hand, regarding to the Wittig olefination route, reported by Subbaraman [13], comprised the coupling components of nonanal (**10**) and the Wittig salt **11**, which were derived from oleic acid and acrolein, respectively. The reaction yield of the key Wittig olefination step was about only 48.5%, which may be somehow limited to be a suitable practical reaction.

Since we are in need of large amount of sex pheromone **1**, (*Z*)-dodec-3-en-1-yl (*E*)-2-butenoate, for the field control application of sweet potato weevil population in integrated pest management (IPM), and the commercial available source is extremely expensive, we have developed an improved synthetic strategy as Method B shown in Scheme 1. Herewith, we wish to report an improved practical synthesis of sex pheromone **1**, as illustrated in Scheme 2. The crucial modifications for this synthesis consist of two key steps. First, the alkylation of 1-decyne (**5**) without using carcinogenic ethylene oxide or HMPA, DMPU, ethylene diamine, or high-pressure ammonia cylinder. Instead, by employing the method reported by Chong et al. [14], the alkylation of 1-lithiated alkyne was carried out in the presence of NaI, serving as a good nucleophile and labile leaving group simultaneously, in refluxing THF. Second, the hydrogenation of the internal alkyne to furnish *cis*-alkene by the stereoselective palladium-catalyzed transfer semihydrogenation, reported by Hua et al. [15], with the use of KOH/DMF as the hydrogen source system.
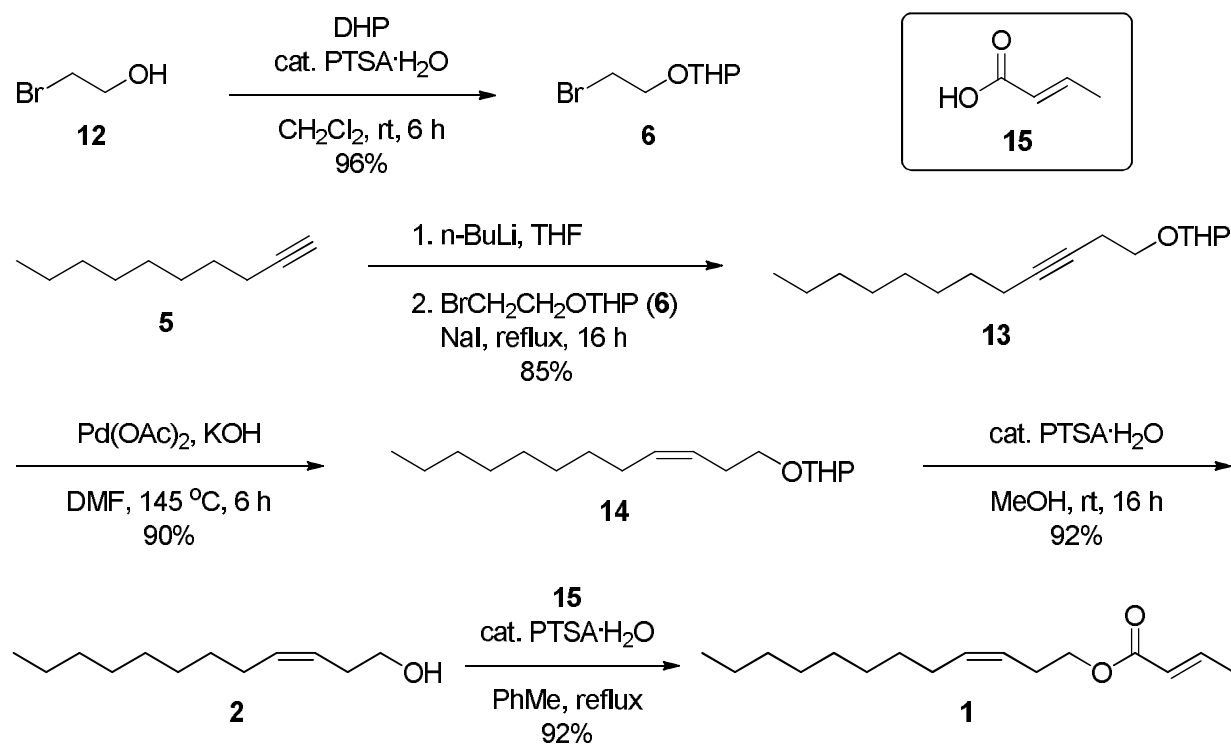
Scheme 2. Improved synthesis of (*Z*)-dodec-3-en-1-yl (*E*)-2-butenoate (**1**)

2. Materials and methods (experimental section)

2.1. General

The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded using a Varian Gemini 200 MHz NMR spectrometer at ambient temperature, and obtained at 200 MHz and 50 MHz, respectively. Chemical shifts (δ) and coupling constants (J) were reported in ppm and hertz (Hz), respectively. Samples for NMR measurements were dissolved in CDCl$_3$. The deuterated solvent residue CHCl$_3$ was used as the internal standard and calibrated at δ 7.26 ppm in ^{1}H NMR spectra and δ 77.0 ppm in ^{13}C NMR spectra, respectively. Multiplicities of splitting patterns were abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). The ^{1}H NMR spectral data were expressed in the following manner: chemical shift (multiplicity, coupling constant, number of hydrogen).

Thin-layer chromatography (TLC) was performed on Merck 25 TLC aluminum sheets (silica gel 60 F$_{254}$). The developed TLC sheets were examined under UV light or by using appropriate TLC stains, e.g. aqueous permanganate (KMnO$_4$), or ethanolic phosphomolybdic acid solutions. Column chromatography was performed on Merck silica gel 60 (70-230 mesh), and Merck silica gel 60 (230-400 mesh) was used for flash column chromatography. Eluent was prepared from two solvents in a stated volume ratio. All solvents used were either reagent grade or were distilled prior to use.

2.2. 2-(2-Bromoethoxy)tetrahydro-2*H*-pyran (6)

To a mixture of 2-bromoethanol (12) (90.06 g, 720.7 mmol) and catalytic amount of *p*-toluenesulfonic acid monohydrate (PTSA·H$_2$O, 1.37 g, 7.20 mmol) in CH$_2$Cl$_2$ (700 mL) was added dropwise 3,4-dihydro-2*H*-pyran (DHP, 63.65 g, 756.7 mmol) at 0 °C. After the addition was complete, the reaction mixture was stirred at 0 °C for 30 min, and then at rt for 6 h. The reaction mixture was washed successively with saturated NaHCO$_3$ solution (150 mL × 3), and brine (300 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The dark brown residue was distilled under reduced pressure (bath temp 100-110 °C, 10 torr) to afford bromo-compound **6** as a colorless oil (144.66 g, 96%). ^{1}H NMR (200 MHz, CDCl$_3$, ppm): δ = 4.72-4.62 (m, 1H), 4.10-3.65 (m, 3H), 3.60-3.42 (m, 3H), 1.95-1.40 (m, 6H); ^{13}C NMR (50 MHz, CDCl$_3$, ppm): δ = 98.9, 67.5, 62.3, 30.8, 30.4, 25.3, 19.2.

2.3. 2-(Dodec-3-yn-1-yloxy)tetrahydro-2*H*-pyran (13)

A solution of 2.5 M *n*-BuLi in hexane (161.0 mL, 402.5 mmol) was introduced dropwise to a solution of 1-decyne (**5**) (45.00 g, 325.5 mmol) in THF (150 mL), stirred under N$_2$ atmosphere, at -78 °C. The reaction mixture was warmed to rt and stirred for 1 h. To this reaction mixture was added solid NaI (6.04 g, 40.3 mmol) and compound **6** (64.80 g, 309.9 mmol) at rt. The resulting mixture was refluxed for 16 h. After cooling to rt, the reaction was quenched with saturated NaHCO$_3$ solution (300 mL), and the organic layer was separated. The aqueous layer was extracted with *n*-hexane (300 mL × 2). The combined organic layer was washed with brine (300 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo to afford alkyne **13** as a light yellow oil (70.18 g, 85%). The crude product was used directly for next reaction without further purification. ^{1}H NMR (200 MHz, CDCl$_3$, ppm): δ = 4.70-4.58 (m, 1H), 3.97-3.70 (m, 2H), 3.60-3.42 (m, 2H), 2.53-2.38 (m, 2H), 2.20-2.05 (m, 2H), 1.95-1.10 (m, 18H), 0.87 (t, J = 6.3Hz,

3H); ^{13}C NMR (50 MHz, CDCl$_3$, ppm): δ = 98.7, 81.4, 76.7, 66.2, 62.1, 31.8, 30.6, 29.2, 29.1, 29.0, 28.8, 25.4, 22.6, 20.2, 19.4, 18.7, 14.1.

2.4. (*Z*)-2-(Dodec-3-en-1-yloxy)tetrahydro-2*H*-pyran (14)

To a mixture of alkyne **13** (12.01 g, 45.1 mmol), ground KOH powder (3.79 g, 67.7 mmol), and Pd(OAc)$_2$ (202.5 mg, 0.9 mmol) in a thick-walled Pyrex seal tube was added degassed DMF (30 mL). The tube was sealed, and the reaction mixture was stirred vigorously at 145 °C for 6 h. After cooling to rt, the cap was opened carefully, and the resulting suspension was passed through a silica gel bed (3 cm) and washed with *n*-hexane (150 mL). The combined filtrate was washed with water (100 mL × 5) to remove DMF. The organic layer was dried over MgSO$_4$, filtered, and concentrated in vacuo to afford alkene **14** as dark brown oil (10.90 g, 90%). The crude product was used directly for next reaction without further purification. ^{1}H NMR (200 MHz, CDCl$_3$, ppm): δ = 5.58-5.25 (m, 2H), 4.65-4.50 (m, 1H), 3.95-3.65 (m, 2H), 3.55-3.30 (m, 2H), 2.35 (q, *J*=6.7Hz, 2H), 2.15-1.90 (m, 2H), 1.90-1.42 (m, 6H), 1.40-1.10 (m, 12H), 0.87 (t, *J* = 6.5Hz, 3H); ^{13}C NMR (50MHz, CDCl$_3$, ppm): δ = 132.0, 125.4, 98.7, 67.1, 62.3, 31.9, 30.7, 29.6, 29.5 (2C), 29.3, 27.9, 27.3, 25.5, 22.7, 19.6, 14.1.

2.5. (*Z*)-Dodec-3-en-1-ol (2)

A mixture of alkene **14** (21.37 g, 79.6 mmol) and PTSA·H$_2$O (0.76 g, 4.0 mmol) in MeOH (150 mL) was stirred at rt for 16 h. After the evaporation of MeOH, the residue was treated with 1 M HCl solution (200 mL) and extracted with *n*-hexane (150 mL × 3). The combined organic layer was washed with brine (300 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo to afford enol **2** as a brown oil (13.50 g, 92%). The crude product was used directly for next reaction without further purification. ^{1}H NMR (200 MHz, CDCl$_3$, ppm): δ = 5.70-5.25 (m, 2H), 3.64 (t, *J* = 6.2Hz, 2H), 2.32 (q, *J* = 6.6Hz, 2H), 2.15-1.90 (m, 2H), 1.75-1.05 (m, 13H), 0.87 (t, *J* = 6.3Hz, 3H); ^{13}C NMR (50 MHz, CDCl$_3$, ppm): δ = 133.6, 124.9, 62.3, 31.9, 30.8, 29.7, 29.5, 29.3, 29.2, 27.4, 22.6, 14.1.

2.6. (*Z*)-Dodec-3-en-1-yl (*E*)-2-butenoate (1)

A mixture of enol **2** (15.34 g, 83.2 mmol), crotonic acid (**15**) (9.56 g, 116.5 mmol), and PTSA·H$_2$O (0.32 g, 1.7 mmol) in PhMe (100 mL) was reflux for 16 h. During the reaction time, water was collected by azeotropic distillation using Dean-Stark apparatus. After cooling to rt, the reaction was quenched with saturated NaHCO$_3$ solution (150 mL), and the organic layer was separated. The aqueous layer was extracted with *n*-hexane (150 mL × 3). The combined organic layer was washed successively with saturated NaHCO$_3$ solution (150 mL) and brine (150 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo to afford the desired ester **1** as a brown residue. The crude residue was subjected to column chromatography (silica gel, 2% EtOAc/hexane) to afford a light yellow oil. Further distillation under reduced pressure (140-145 °C, 10 torr) gave ester **1** as a colorless oil (17.64 g, 84%). ^{1}H NMR (200 MHz, CDCl$_3$, ppm): δ = 6.96 (dq, *J* = 15.6, 6.9 Hz, 1 H), 5.83 (dq, *J* = 15.6, 1.2 Hz, 1H), 5.60-5.25 (m, 2H), 4.11 (t, *J* = 6.9 Hz, 2H), 2.39 (q, *J* = 6.8 Hz, 2H), 2.15-1.92 (m, 2H), 1.87 (dd, *J* = 1.2, 6.9 Hz, 3H), 1.45-1.15 (br s, 12H), 0.87 (t, *J* = 6.4Hz, 3H); ^{13}C NMR (50 MHz, CDCl$_3$, ppm): δ = 166.6, 144.5, 132.9, 124.3, 122.7, 63.7, 31.9, 29.6, 29.5, 29.3 (2C), 27.3, 26.9, 22.6, 17.9, 14.1.

2.7. Field Tests

Fielding testing were carried out in Siluo township, Yunlin county, during September 6-September 13, 2011. Other samples for field test comparison were provided by Zhangzhou Enjoy Agriculture Technology Co., Ltd., China, and by Professor Yao-Pin Yen, Department of Applied Chemistry, Providence University, Taiwan. Each sample, including blank control, was applied to 4 replicated traps. All traps were set 15 m apart randomly from each other, and were rotated regularly every 2 days.

3. Results and Discussion

As illustrated in Scheme 2, the synthesis began with the conventional hydroxyl group protection of 2-bromoethanol (**12**) with DHP in the presence of catalytic amount of PTSA. The corresponding tetrahydropyranyl ether **6** was afforded in excellent yield. The lithiation of 1-decyne (**5**) was achieved by the treatment of *n*-BuLi to form the lithium acetylide.

To this acetylide intermediate was added solid NaI [14] and bromo compound **6** in one portion, and the reaction mixture was reflux for 16 h to afford the corresponding alkyne **13** in 85% yield. It was gratifying to discover that the reaction is allowed to carry out in more concentrated conditions, ca. 2 M. However, a more condensed concentration is not recommended since the composition of nonpolar *n*-hexane is increased, which may decrease the rate of alkylation.

Although the hydrogenation, using molecular hydrogen in the presence of Lindlar's catalyst, of internal alkyne to form *cis*-alkene is a well-accepted method for this transformation, the operation required a well-trained technician with good laboratory skills. In addition, the hydrogenation with molecular hydrogen catalyzed by Lindlar's catalyst sometimes accompanied with over-reduction problem.

We prefer to utilize the safe hydrogenation process with competitive stereoselectivity. The palladium-catalyzed transfer semihydrogenation of alkyne **13** was performed in the presence of 2 mol% of Pd(OAc)$_2$ and 1.5 equiv of KOH in DMF, ca. 1.5 M. The reaction mixture was sealed in a thick-walled seal tube and heated to 145 °C for 6 h with vigorously stirring [15], and the desired *cis*-alkene **14** was isolated as a sole isomer in 90% yield.

It was found that both fresh distilled DMF and undried DMF gave excellent yields, and the purging with nitrogen was not necessary. In addition, when the reaction was performed at 120 °C for 16 h under ambient pressure, the crude NMR spectrum showed only trace amount of starting material, however, with lower product purity.

Deprotection of alkene **14** in the presence of catalytic amount of PTSA in MeOH at rt furnished enol **2** in 92% yield. Treatment of enol **2** with crotonic acid (**15**) underwent Fischer esterification in the presence of PTSA in refluxing toluene [16], and water was removed by azeotropic distillation using Dean-Stark apparatus. After the isolation of crude ester **1**, further purification using column chromatography and vacuum distillation afforded pure sex pheromone **1** as a colorless oil in 92% yield.

The sex pheromone **1** synthesized was then subjected to lure preparation and field tests, and was compared with the samples provided by Zhangzhou Enjoy Co. and Yen group. The results of field tests, as shown in Table 1, indicated that all three synthetic sex pheromone samples were equally effective for field trapping. Moreover, based on the result of field tests, the sex pheromone **1** synthesized according to our methodology consists of no repellent chemical to sweet potato weevil.

Table 1. Field tests on the attraction of male sweet potato weevil using different sources of sex pheromone **1**

Attractant Entry	Sex Pheromone Source			
	Blank	This Work	Yen	Zhangzhou Enjoy Co., Ltd.
1	4	186	171	185
2	5	164	162	171
3	4	178	177	167
Total Male Attracted	13	528	510	523

4. Conclusion

In summary, we have developed an improved synthesis of (*Z*)-dodec-3-en-1-yl (*E*)-2-butenoate (**1**), the female sex pheromone of sweet potato weevil. The modified procedures consist of 5 steps with a total yield of 62%. The green reaction conditions were applied to the alkylation of terminal alkyne **5** with alkyl bromide by using NaI in refluxing THF. A highly stereoselective palladium-catalyzed transfer semihydrogenation, using KOH/DMF as the hydrogen source, was utilized to convert internal alkyne **13** into *cis*-alkene **14** in excellent yield. The sex pheromone **1**, synthesized by our methodology, showed competitive effectiveness in field testing experiments.

Acknowledgements

References

[1] Loebenstein, G. and Thottappilly, G. 2009. *"The Sweetpotato"*. Springer. Netherlands.

[2] FAOSTAT. 2006. "*Food Production Yearbook*". Food and Agriculture Organization, Rome, Italy.

[3] Council of Agriculture. 2010. "*Yearly Report of Taiwan's Agriculture*". Council of Agriculture, Executive Yuan, Taiwan, R. O. C.

[4] Sutherland, J. A. 1986. A review on the biology and control of the sweetpotato weevil, *Cylas formicarius* (Fab). *Tropical Pest Management*, 32: 304-315.

[5] Sureda, T., Quero, C., Bosch, M. P., Avilés, R., Coll, F., Renou, M., and Guerrero, A. 2006. Electrophysiological and behavioral responses of a Cuban population of the sweet potato weevil to its sex pheromone. *Journal of Chemical Ecology*, 32: 2177-2190.

[6] Reddy, G. V. P., Gadi, N., and Taianao, A. J. 2012. Efficient sex pheromone trapping: catching the sweetpotato weevil, *Cylas formicarius*. *Journal of Chemical Ecology*, 38: 846-853.

[7] Heath, R. R., Coffelt, J. A., Sonnet, P. E., Proshold, F. I., Dueben, B., and Tumlinson, J. H.

1986. Identification of sex pheromone produced by female sweetpotato weevil, *Cylas formicarius elegantulus* (SUMMERS). *Journal of Chemical Ecology*, 12: 1489-1503.

[8] Talekar, N. S. and Lee, S. T. 1989. Studies on the utilization of a female sex pheromone for the management of sweetpotato weevil, *Cylas formicarius* (F.) (Coleoptera: Curculionidae). *Bulletin of the Institute of Zoology, Academia Sinica*, 28: 281-288.

[9] Yen, Y. P. and Hwang, J. S. 1990. Improved synthesis method and bioactivity of sex pheromone of sweetpotato weevil, (*Cylas formicarius elegantulus* (SUMMERS)). *Plant Protection Bulletin*, 32: 239-241.

[10] Liu, J. and Li, Z. 2001. Total synthesis of sweet potato weevil *Cylas formicarius fabricius* sex pheromone (*Z*)-3-dodecen-1-yl (*E*)-2-butenoate. *Chinese Journal of Applied Chemistry*, 18: 998-1000.

[11] Lo, C. C., Hung, M. D., and Liu, C. J. 1992. Replacement of carcinogenic alkylating agent ethylene oxide in the synthesis of (*Z*)-3-dodecen-1-yl (*E*)-2-butenoate, sex pheromone of sweet-potato weevil, *Cylas formicarius elegantulus* (SUMMERS) and *Cylas formicarius formicarius* (F.). *Journal of Chemical Ecology*, 18: 95-103.

[12] Carvalho, J. F. and Prestwich, G. D. 1984. Synthesis of ω-tritiated and ω-fluorinated analogues of the trail pheromone of subterranean termites. *The Journal of Organic Chemistry*, 49: 1251-1258.

[13] Mithran, S. and Subbaraman, A. S. 1999. Synthesis of (3*Z*)-dodecenyl-(*E*)-2-butenoate, the pheromone of sweet potato weevil. *Molecules*, 4: 159-164.

[14] Buck, M. and Chong, J. M. 2001. Alkylation of 1-alkynes in THF. *Tetrahedron Letters*, 42: 5825-5827.

[15] Li, J., Hua, R. and Liu, T. 2010. Highly chemo- and stereoselective palladium-catalyzed transfer semihydrogenation of internal alkynes affording *cis*-alkenes. *The Journal of Organic Chemistry*, 75: 2966-2970.

[16] Miyoshi, Y., and Takehiko, F. 2008. Method for preparing higher alcohol crotonates. Shin-Etsu Chemical, Oct 22nd, 2008: CN 200810006570; Nov 6th, 2008: JP 2008-266150; Feb 16th, 2009: TW 097112458.