Concise Syntheses of (7Z,11Z,13E)-Hexadecatrienal and (8E,18Z)-Tetradecadienal

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Abstract: Concise and efficient syntheses of (7Z, 11Z, 13E)-hexadecatrienal, a sex-pheromone component of the citrus leaf miner, and (8E, 10Z)-tetradecadienal, the sex pheromone of the horse-chestnut leaf miner were described, starting from the commercially available acetylene and acrolein. The stereoselective formation of *E*,*Z*-conjugated double bond relied on cross-coupling between Grignard reagent and (E,Z)-bromodiene. The present syntheses achieved high overall yield (26% of the former and 23% for the latter) and high isomeric purity (97% for the former and 99% for the latter).

Key words: (7*Z*,11*Z*,13*E*)-hexadecatrienal, (8*E*,10*Z*)-tetradecadienal, 7-bromo-(4*Z*,6*E*)-heptadienal, Kumada cross-coupling, hydroboration–oxidation

The citrus leaf miner, *Phyllocnistis citrella* Stainton, is an important pest of citrus and related Rutaceae almost worldwide.¹ Damages caused by the citrus leaf miner include loss of photosynthetic capacity from mining, stunting, and malformation of leaves.^{2a} Besides those damages, the larval mining increases the susceptibility of trees to the citrus canker disease, caused by *Xanthomonuas axonopodis pv citri*.²

Effective chemical control of the citrus leaf miner is difficult to achieve since the feeding larvae and pupae are protected by the leaf cuticle and the rolled leaf margins.³ Moreover, the general utility of insecticides is limited by high cost, persistence of residue in tubers, and the environment and development of this insecticide-resistant pest. Considerable efforts have been made for the development and evaluation of new integrated pest-management techniques. So the development of new integrated pest-management techniques with pheromone compounds is a very desired goal.³ The semiochemicals of the pest have been identified as (7Z, 11Z, 13E)-hexadecatrienal (1, Figure 1), (7Z,11Z)-hexadecadienal, and (7Z)hexadecenal in a ratio of 30:10:1, respectively.⁴ Recently, the synthetic sex pheromone has been used in control of the pest via mass trapping and mating disruption techniques.2a,4,5

SYNLETT 2012, 23, 581–584 Advanced online publication: 08.02.2012 DOI: 10.1055/s-0031-1290338; Art ID: W57511ST © Georg Thieme Verlag Stuttgart · New York A few of the syntheses of (7Z,11Z,13E)-hexadecatrienal (1) were developed, and the reported synthetic routes to the pheromone are complicated.^{4,5a,6} Leal et al. achieved the synthesis of the pheromone by employing the C6+C5+C5 strategy.⁴ The introduction of the 7Z double bond in this synthesis was achieved by cross-coupling between suitable haloalkane and lithioalkyne and subsequent stereoselective reduction; The introduction of 11Z,13E-conjugated double bonds was achieved by the Wittig reaction as the key step. Another synthesis of the pheromone reported by Ando et al. (C7+C4+C5 strategy), employing the Wittig reaction as the key step.⁶ However, these methods do not afford a product with high enough chemical or isomeric purity.

The horse chestnut leaf miner, *Cameraria Ohridella*, is a new pest that is causing more and more damage in horse chestnut trees⁷ and it is found throughout Europe.⁸ The most obvious damage consists of course of the mines caused by larvae. This can evolve to such an extent that leaves turn brown and fall off prematurely.⁷

The control of the horse chestnut leaf miner with chemical products is very difficult since it lives inside the leaf mines during most of its life cycle. Furthermore, in some countries, strict regulations about pesticide use limit the number of chemical products that can be used against this pest. Thus biological alternatives will become more and more important in the future.⁷ (8*E*,10*Z*)-Tetradecadienal (2) was identified by Svatos et al. as the female sex pheromone of the horse chestnut leaf miner.^{9a} Recently, the synthetic sex pheromone has been used in integrated management of the pest.⁷

The reported synthetic routes to (8E,10Z)-tetradecadienal (2) were based on both strategies including reduction of enyne precursor^{8,9} and Wittig-type olefination.^{10,11} The first synthesis of **2** was achieved via reduction of (6E)-14-(tert-butoxy)tetradecen-4-yne, which was prepared by Sonogashira cross-coupling of 1-iodo-9-(tert-butoxy)-(1E)-nonene with 1-pentyne.⁹ Although the strategy can afford a product with high enough chemical or isomeric purity, preparation of 1-iodo-9-(tert-butoxy)-(1E)-nonene, the key intermediate of the Sonogashira protocol, is complicated and expensive (via five steps from 1,7-heptanediol). Recently, Grodner developed a new synthesis

of aldehyde **2** based on reduction of enyne precursor, which was prepared using Pd(0)-catalyzed cross-coupling of Grignard reagent with the corresponding vinyl iodides.⁸ Another synthetic strategy of aldehyde **2** was reported by Francke et al., employing the Wittig reaction as the key step.¹⁰ Christmann et al. reported a synthesis of aldehyde **2** using a combination of two Wittig reactions.¹¹ However, a relatively low isomeric purity of the product and a high cost of removal of triphenylphosphine oxide make both strategies less desirable alternatives, considering the potential commercial application.

Considering that both pheromones are increasingly used in large-scale field tests, the development of the concise, cost-effective, and operationally simple synthetic approaches is necessary. Previously, we reported an efficient synthesis of (5Z,7E)-dodecadien-1-ol, the sex pheromone of *Dendrolimus Spp.*, from aldehyde **3**.¹² As a part of an ongoing program, we report herein concise and stereoselective syntheses for (7Z,11Z,11E)-hexadecatrienal (**1**) and (8E,10Z)-tetradecadienal (**2**) from aldehyde **3**, which successfully overcome the major limitations of the strategies published previously. In both syntheses, *E*,*Z*conjugated double bonds of **1** and **2** were achieved by cross-coupling between Grignard reagents and (E,Z)-bromodienes.



Figure 1

Bromide **6**, an important intermediate for both syntheses, was firstly prepared from 4-bromobutan-1-ol (**4**, Scheme 1). Alcohol **4** in THF was treated with 2.1 equivalents of allylmagnesium chloride in the presence of dilithium tetrachlorocuprate to give 6-hepten-1-ol (**5**), which was treated with triphenylphosphine–bromine complex in acetonitrile to afford 7-bromohept-1-ene (**6**). The bromide was heated with triphenylphosphane in acetonitrile to furnish phosphonium salt **7** in 71% overall yield based on **4** (3 steps).¹³



Scheme 1 Reagents and conditions: (a) $CH_2=CHCH_2MgCl$ (2.1 equiv), Li_2CuC1_4 (20 mol%), THF, r.t., 15 h (90%); (b) Ph₃P, Br₂, MeCN, -10 °C, 1 h (85%); (c) Ph₃P, MeCN, 80 °C, 48 h (93%).

(7Z,11Z,13E)-Hexadecatrienal (1) was synthesized by an unambiguous stereoselective route, as outlined in Scheme 2. 7-Bromo-(4Z,6E)-heptadienal (3) was prepared in 50% yield by the tandem addition reaction of ac-

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rolein with acetylene in the presence of $Pd(OAc)_{2}$.¹⁴ Aldehyde 3 is so pure as to be used in the next step without purification by column chromatography. The construction of the 7Z double bond relied on the Wittig reaction. To ensure cis selectivity of this Wittig olefination, potassium bis(trimethylsilyl)amide was chosen as the base. The ylide, prepared from phosphonium salt 7 by treatment with potassium bis(trimethylsilyl) amide as base in dry THF at -78 °C, reacted with aldehyde 3 to afford tetraene 8 in 85% yield and 98% isomeric purity.^{15,16} Kumada cross-coupling of tetraene 8 with ethylmagnesium bromide via catalysis of NiCl₂(dppp) in dry THF at room temperature gave tetraene 9 in 93% yield and 97% isomeric purity.^{17,18} Kumada cross-coupling maintain the excellent isomeric purity owing to the moderate conditions. Tetraene 9 was transformed into alcohol 10 via the 9-BBN-H₂O₂ system in 80% yield.¹⁹ Due to the high regioselectivity of the 9-BBN-H₂O₂ system, this reaction gave less than 1% of the secondary alcohol byproduct as measured by GC. In the final step, (7Z,11Z,13E)-hexadecatrienal (1) was prepared by oxidation of alcohol 10 using pyridinium chlorochromate/Celite in dichloromethane in 83% yield.¹⁵ The overall yield of the target product **1** from aldehyde 3 was 52%; the overall yield of the product 1from acrolein was 26%. Since aldehyde 3 is a highly stereodefined compound (the isomeric purity >99%) and the Wittig reaction achieves 98% isomeric purity, the present synthesis achieved high stereoselectivity (97% isomeric purity).



Scheme 2 *Reagents and conditions*: (a) phosphonium salt **7**, KN[Si(Me)₃]₂, THF, -78 °C, 12 h (85%); (b) EtMgBr, cat. NiCl₂(dppp), THF, r.t., 12 h (93%); (c) (i) 9-BBN, r.t., 60 min; (ii) H₂O₂–NaOH, 1.5 h (80%); (d) PCC/Celite, CH₂Cl₂, r.t., 5 h (83%).

In the synthesis of (8E,10Z)-tetradecadienal, aldehyde **3** was treated with zinc-modified cyanoborohydride and (*p*-tolylsulfonyl)hydrazine in methanol to afford diene **11** in 72% yield (Scheme 3).^{20,21} Kumada cross-coupling of diene **11** with (6-hepten-1-yl)magnesium bromide prepared from bromide **6** in dry THF at room temperature gave triene **12** in 91% yield and 99% isomeric purity.^{17,22} Triene **12** was transformed into alcohol **13** via hydroboration–oxidation in 85% yield as described before.¹⁹ In the final step, (8*E*,10*Z*)-tetradecadienal (**2**) was also prepared by oxidation of alcohol **13** in 84% yield as described be-

fore.¹⁵ The overall yield of the target product 2 from aldehyde 3 was 47%; the overall yield of the product 2 from acrolein was 23%. Because of the high isomeric purity of aldehyde 3, the present synthesis achieved a high stereoselectivity (99% isomeric purity).



Scheme 3 Reagents and conditions: (a) $TsNHNH_2/ZnCl_2-NaBH_3CN$, MeOH, 65 °C, 2 h (72%); (b) hept-6-enyl -magnesium bromide, cat. NiCl_2(dppp), THF, r.t., 12 h (91%); (c) (i) 9-BBN, r.t., 60 min; (ii) H_2O_2 -NaOH, 1.5 h (85%); (d) PCC/Celite, CH_2Cl_2 , r.t., 5 h (84%).

Both synthetic approaches employed low-cost reagents, familiar operation, and mild conditions, thus the present strategies may become a more desirable alternative for both target products in high stereoselectivity and high yield. The simplicity and the low cost of the present syntheses suggest the potentially practical use of the above pheromones in integrated management programs for both serious insect pests.

In summary, we have developed highly efficient and stereoselective syntheses of (7Z,11Z,13E)-hexadecatrienal (1) and (8E,10Z)-tetradecadienal (2) with very good overall yield. The stereoselective formation of *E*,*Z*-conjugated double bond relied on cross-coupling between Grignard reagent and (E,Z)-bromodiene.

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- (16) Preparation for Tetraene 8 Potassium bis(trimethylsilyl) amide (75 mL, 75 mmol, 1 M solution in THF) was added dropwise over 30 min to a suspension of freshly prepared phosphonium salt 7 (33 g, 75 mmol) in dry THF (75 mL) at 0 °C, under nitrogen. The resulting orange solution was stirred for 1 h at 0 °C and then cooled to -78 °C. A solution of aldehyde 3 (9.5 g, 50 mmol) in dry THF (100 mL) was added dropwise over 1 h, maintaining the temperature below -70 °C. The resulting yellow solution was allowed to warm slowly to r.t. over a period of 3 h and left overnight. Then the reaction mixture was quenched with a sat. solution of NH₄Cl (150 mL). After THF was removed by evaporation, the reaction mixture was extracted with PE (3×40 mL). The extract was washed with $\mathrm{H_2O}$ and brine, dried over $\mathrm{Na_2SO_4},$ and concentrated. The residue was purified through a silica gel column (eluent: PE) to afford tetraene 8 as a colorless oil (11.48 g, 85%, isomeric purity >98%, chemical purity 96%). ¹H NMR (500 MHz, $CDCl_3$): $\delta = 6.97 (ddd, J = 13.3, 11.6, 1.2 Hz, 1 H, CH=CH),$ 6.32 (dd, J = 13.3, 1.3 Hz, 1 H, CH=CH), 5.93 (ddd, *J* = 11.6, 11.1, 1.3 Hz, 1 H, CH=CH), 5.80 (ddt, *J* = 17.1, 10.1 Hz, 1 H, CH=CH₂), 5.43-5.23 (m, 3 H, CH=CH,), 4.98 (d, J = 17.1 Hz, 1 H, Z-CH=CH₂), 4.92 (d, J = 10.1 Hz, 1 H, *E*-CH=CH₂), 2.15–1.95 (m, 8 H, CH₂), 1.42–1.32 (m, 4 H, CH₂CH₂). ¹³C NMR (125 MHz, CDCl₃): δ = 139.3, 133.2, 131.4, 128.9, 128.3, 126.5, 114.6, 109.3, 33.4, 29.5, 28.9, 28.4, 27.5, 26.8. ESI-HRMS: *m/z* calcd for C₁₄H₂₁Br [M]⁺: 268.0827; found: 268.0812.
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- (18) **Preparation for Tetraene 9**
 - A solution of tetraene **8** (10.72 g, 40 mmol) and NiCl₂(dppp) (54.2 mg, 0.1 mmol) in dry THF (40 mL) was stirred at r.t. for 30 min under an argon atmosphere. EtMgBr (60 mmol) in dry THF (60 mL) was added to the mixture cooled in an ice bath over 30 min. The nickel complex reacts immediately with the Grignard reagent, and the resulting clear-tan reaction mixture is allowed to warm up to r.t. with stirring for 12 h. After the reaction was completed, the mixture was poured into H₂O. After THF was removed by evaporation, the reaction mixture was extracted with PE (3 × 30 mL). The extract was washed with H₂O and brine, dried over Na₂SO₄,

and concentrated. The residue was purified through a silica gel column (eluent: PE) to afford tetraene **9** as a colorless oil (8.11 g, 93%, isomeric purity >97%, chemical purity 96%). ¹H NMR (500 MHz, CDCl₃): $\delta = 6.30$ (ddd, J = 15.0, 11.0, 1.0 Hz, 1 H, CH=CH), 5.99 (ddd, J = 11.0, 10.7, 1.1 Hz, 1 H, CH=CH), 5.80 (ddt, J = 17.1, 10.1 Hz, 1 H, CH=CH₂), 5.71 (dtd, J = 15.0, 7.5, 1.1 Hz, 1 H, CH=CH), 5.46–5.26 (m, 3 H, CH=CH), 4.99 (d, J = 17.1 Hz, 1 H, Z-CH=CH₂), 4.93 (d, J = 10.1 Hz, 1 H, *E*-CH=CH₂), 2.15–1.95 (m, 10 H, CH₂), 1.42–1.32 (m, 4 H, CH₂CH₂), 1.02 (t, 3 H, J = 7.5 Hz, CH₃). ¹³C NMR (125 MHz, CDCl₃): $\delta = 139.4, 136.8, 130.3, 129.7, 129.5, 129.4, 125.1, 114.6, 33.1, 29.6, 29.0, 28.3, 27.8, 27.5, 26.3, 14.0. ESI-HRMS:$ *m/z*calcd for C₁₆H₂₆ [M]⁺: 218.2035; found: 218.2023.

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- (21) Spectral Data for Diene 11 ¹H NMR (500 MHz, CDCl₃): $\delta = 6.97$ (ddd, J = 13.3, 11.6,

1.2 Hz, 1 H, CH=CH), 6.26 (dd, J = 13.3, 1.3 Hz, 1 H, CH=CH), 5.89 (ddd, J = 11.6, 11.1, 1.3 Hz, 1 H, CH=CH), 5.47 (dtd, J = 11.1, 7.5, 1.2 Hz, 1 H, CH=CH), 2.10 (m, 2 H, CH₂), 1.42 (m, 2 H, CH₂), 0.90 (t, J = 7.5 Hz, 3 H, CH₃). ¹³C NMR (125 MHz, CDCl₃): $\delta = 133.5$, 133.3, 125.9, 108.6, 29.9, 22.6, 13.7. ESI-HRMS: m/z calcd for C₇H₁₁Br [M]⁺: 174.0044; found: 174.0062.

(22) Spectral Data for Triene 12

¹H NMR (500 MHz, CDCl₃): $\delta = 6.30$ (ddd, J = 15.0, 11.0, 1.0 Hz, 1 H, CH=CH), 5.99 (ddd, J = 11.0, 10.7, 1.1 Hz, 1 H, CH=CH), 5.80 (ddt, J = 17.1, 10.1 Hz, 1 H, CH=CH₂), 5.65 (dtd, J = 15.0, 7.5, 1.1 Hz, 1 H, CH=CH), 5.30 (dtd, J = 10.7, 7.5, 1.0 Hz, 1 H, CH=CH), 4.99 (d, J = 17.1 Hz, 1 H, Z-CH=CH₂), 4.93 (d, J = 10.1 Hz, 1 H, E-CH=CH₂), 2.15–2.00 (m, 6 H, CH₂), 1.42–1.32 (m, 8 H, CH₂CH₂), 0.9 (t, 3 H, J = 7.5 Hz, CH₃). ¹³C NMR (125 MHz, CDCl₃): $\delta = 139.5, 134.9, 130.8, 130.3, 126.1, 114.6, 34.1, 32.9, 32.3, 30.1, 29.7, 29.1, 23.1, 14.1. ESI-HRMS: <math>m/z$ calcd for C₁₄H₂₄ [M]⁺: 192.1878; found: 192.1861.

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