New Synthesis of (11Z,13Z)-11,13-Hexadecadienal, the Female Sex Pheromone of the Navel Orangeworm*

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Among these six syntheses, four of them introduced the formyl group by final oxidation of 1-hexadecadienol with either pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC). Bishop and Morrow recorded a synthesis of 2.8 kg of 1, in which the formyl group was introduced into their intermediate as a diethyldelactyl, and final deprotection afforded 1. Furber and Taylor also employed diethyldelactyl intermediates in their synthesis of 1.

The construction of the (Z,Z)-conjugated diene system has been achieved in the past by a number of different protocols: the Wittig reaction coupled with partial hydrogenation of acetylene, hydroboration-protonolysis of 1,3-diyne, diimide reduction of acetylene and palladium-catalyzed coupling, organocopper chemistry, palladium-catalyzed coupling and hydroboration-protonolysis, and copper-catalyzed Grignard coupling and hydroboration-protonolysis.

A critical examination of all the published syntheses indicates that the preparation of 1 in a multi-gram-scale was not an easy task due to the non-reproducibility of some of the earlier works. This paper reports my experimental result, which gives a multi-gram quantity of 94–95% pure 1.

Results and Discussion

Scheme 1 shows the synthetic plan for 1. Sonogashira-Hagihara coupling of (Z)-1-bromo-1-butene (A) with 1,1-dioctoxy-1-dodecyn (B) will give the required carbon-skeleton as (Z)-1,1-dioctoxy-13-hexadecene-11-yne, whose selective reduction and deprotection will give 1. Bromoalkene A is readily available from (E)-2-pentenoic acid (C), while B can be prepared from 10-iododecanal (D).

The new eight-step-synthesis of (11Z,13Z)-11,13-hexadecadienyl (I) is summarized in Scheme 2. Commercially available 10-bromo-1-decanol (2) was chosen as the starting material. Since a GC-MS analysis of 2 revealed the presence of a few percent of 1,10-dibromodecan in it, 10-iodo-1-decanol (3) obtained by treating 2 with sodium iodide in acetone was purified by chromatography to give pure monoiode 3 in an 87% yield. PCC oxidation of 3 gave crystalline aldehyde 4 in 74% yield. This was treated with triethyl orthoformate and p-toluene sulfonic acid in diethyl ether to give 5 in 91% yield. Alkylation of lithium

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trimethylsilylacetylide with 5 in THF/HMPA furnished 6 in a quantitative yield. (The use of 10-bromo-1,1-diethoxydecane instead of 5 generated impure 6 contaminated with 5–10% of starting bromide. This eventually resulted in contamination of final product 1 with 5–10% of inseparable 10-bromodecanal.) Desilylation of 6 with potassium carbonate in methanol afforded 1,1-dioxy-11-dodecyne 7 in an 82% yield.

The next step involved coupling 7 with 8 under the Sonogashira-Hagihara conditions. 9,10) (Z)-1-Bromo-1-butene (8) prepared by decarboxylative dehydrobromination of trans-2,3-dibromopentanoic acid 11 was pure enough [97% of 8 with 3% of its (E)-isomer] immediately after its preparation. Even in a cold and dark refrigerator, however, it isomerized after a month to give a mixture of 8 and its (E)-isomer (61:38) as analyzed by GC-MS. It was therefore important to use freshly prepared 8 for the coupling reaction. This isomerization may have been due to a carbocation-mediated process, because a very faint fume of hydrogen bromide could be seen when the storage bottle was opened.

Sonogashira-Hagihara coupling of 7 with 8 in benzenene/n-propylamine was successfully achieved in the presence of 2.4 mol% of tetrakis(triphenylphosphine)-palladium(0) and 8.3 mol% of copper(I) iodide. The reaction was slightly exothermic, and gave 9 in a quantitative yield after chromatographic purification. This coupling reaction was highly reproducible. It must be added that Sonogashira-Hagihara coupling is still being intensively studied, 13) and a new application to pheromone synthesis has been published. 14)

Z-selective reduction of the triple bond of 9 was the next problem. This reduction was first attempted by the method reported by Hungerford and Kitching employing titanium(II). 15) Unfortunately, the reduction was not a clean process, but gave additional products generated by 1,4-reduction of the enyne system of 9. Consequently, hydroboration-protonolysis was applied to reduce the triple bond to a (Z)-double bond. As noted previously by Sonnet and Heath, 4) disiamylborane did not effect complete hydroboration, and therefore dicyclohexylborane was employed. It was found that 3–4 equivalents of dicyclohexylborane in THF were necessary to effect complete hydroboration of the triple bond within 1–2 h. No over-reduction was apparent, probably because the presence of an extremely bulky dicyclohexylboryl group on the carbon chain prevented the approach of the second dicyclohexylborane to attack the double bond. The borane was treated with acetic acid to achieve protonolysis, and the mixture was poured into ice-cooled aqueous sodium hydroxide. Subsequently, hydrogen peroxide was added to the ice-cooled mixture, and the mixture was worked up for 10 min to give 10 and cyclohexanol. The mixture also contained 1, which was liberated in the course of protonolysis with acetic acid. This was purified by chromatography to remove the cyclohexanol.

The resulting mixture of 1 and 10 was dissolved in THF and treated with aqueous oxalic acid to deprotect the acetal moiety and give (11Z,13Z)-11,13-hexadecadienal 1 in a 56% yield based on 9. The foregoing synthesis could be repeated several times without any problem to give 1–3 g of 1. The IR, 1H- and 13C-NMR, and MS data for synthetic pheromone 1 were identical to those reported previously. 13) The purity of 1 was analyzed by GC-MS, and the sample consisted of 94.45% of (11Z,13Z)-1, 2.75% of its (11Z,13E)-isomer and 0.62% of the (11E,13Z)-isomer. It was assumed that our GC column (phenylmethylsiloxane) gave the same order of the retention times for 1 and its isomers as reported by Sonnet and Heath with their cholesterol cinnamate column. 4)

Conclusion

A scalable eight-step-synthesis of (11Z,13Z)-11,13-hexadecadienal, the female sex pheromone of the navel Orangeworm.
orangeworm (Amyelois transitaelli), was achieved in a 27% overall yield by starting from 10-bromo-1-decanol. The present procedure will be useful in manufacturing the economically important pheromone lure against *A. transitaelli*.

**Experimental**

**General.** Refractive indices (n<sub>D</sub>) were measured with an Atago DMT-1 refractometer, and IR spectra with a Jasco FT/IR-410 spectrometer. 1H-NMR spectra (400 MHz, TMS as an internal standard) and 13C-NMR spectra (100 MHz, CDCl<sub>3</sub> at δ = 77.0 as an internal standard) were recorded by a Jeol JNM-AL 400 spectrometer. GC-MS data were measured with an Agilent Technologies 5975 inert XL XL mass spectrometer. HRMS data were recorded by a Jeol JMS-SX 102A instrument. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734.

10-Iododecan-1-ol (3). Powdered sodium iodide (45 g, 300 mmol) was added to a stirred solution of 1 (25 g, 105 mmol) in acetonitrile (200 mL) to make a homogeneous solution. This solution was then stirred and heated under reflux for 4 h. A colorless precipitate of sodium bromide separated from the mixture. The mixture was concentrated in vacuo, diluted with water, and extracted with diethyl ether. The ether layer was successively washed with water, a 1% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo. Water (0.5 mL) was then added to destroy the excess triethylamine. A suspension of pyridinium chlorochromate (PCC, 23.7 g, 110 mmol) in dichloromethane (50 mL) was added dropwise in the course of 30 min to a solution and brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo, as an internal standard) were recorded by a Jeol JNM-AL 400 spectrometer. GC-MS data were measured with an Agilent Technologies 5975 inert XL mass spectrometer. HRMS data were recorded by a Jeol JMS-SX 102A instrument. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734.

10-Iododecan-1-ol (3). A solution of 3 (25.5 g, 90 mmol) in dry dichloromethane (300 mL) was added dropwise in the course of 30 min to a suspension of pyridinium chlorochromate (PCC, 23.7 g, 110 mmol) and Celite (30 g) in dry dichloromethane (350 mL) while vigorously stirring and ice-cooling at 5–15 °C. Stirring was continued for 45 min after this addition. The mixture was then filtered, and the Celite layer was washed with dichloromethane. The combined filtrate and washings were concentrated in vacuo. The dark-colored residue was chromatographed over SiO<sub>2</sub> (120 g). Elution with hexane/ EtOAc (10:1) gave 3.03 g of 1,10-diiododecane derived from contaminating 1,10-dibromodecane. Further elution with hexane/EtOAc (10:1) afforded 25.6 g (87%) of 3 as a colorless oil which slowly solidified to give colorless crystals, mp 48–50 °C.

1.1-Diethoxy-10-iododec-13-en-11-yne (5). Triethyl orthoformate (14.8 g, 100 mmol) and p-toluenesulfonic acid monohydrate (0.2 g, 1 mmol) were added to a stirred and cooled solution of 4 (18.5 g, 65.6 mmol) in dry diethyl ether (25 mL). After the exothermic reaction had subsided, the mixture was left to stand overnight in a refrigerator. Water (0.5 mL) was then added to destroy the excess triethyl orthoformate, and the mixture was made basic by adding a sodium hydrogen carbonate solution. This basic solution was extracted with diethyl ether, and the resulting extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo. The residue (24.4 g) was chromatographed over SiO<sub>2</sub> (80 g). Elution with hexane/EtOAc (25:1) gave 5 (21.2 g, 91%) as a colorless oil, n<sub>D</sub><sup>20</sup> 1.4412; IR (film cm<sup>−1</sup>) 3363 (m, N-H), 3257 (w, O=C–H), 2976 (s), 2929 (s), 2856 (s), 2175 (m, C=C), 1128 (s, C–O), 1067 (m); NMR (CDCl<sub>3</sub>): 1.24–1.44 (13H, m), 1.52–1.60 (2H, m), 1.82 (2H, m), 3.19 (2H, t, J<sub>2, 3</sub> = 7.2), 3.64 (2H, t, J<sub>2, 3</sub> = 7.2), 3.49 (2H, dq, J<sub>6, 7</sub> = 7.2, 3.49 (2H, dq, J<sub>6, 7</sub> = 7.2), 2.24–2.46 (4H, m), 3.49 (2H, dq, J<sub>6, 7</sub> = 7.2), 3.49 (2H, dq, J<sub>6, 7</sub> = 7.2), 2.24–2.46 (4H, m), 3.49 (2H, dq, J<sub>6, 7</sub> = 7.2), 3.49 (2H, dq, J<sub>6, 7</sub> = 7.2), 2.24–2.46 (4H, m), 3.49 (2H, dq, J<sub>6, 7</sub> = 7.2). NMR (CDCl<sub>3</sub>): 1.25–1.45 (12H, m), 1.48–1.56 (2H, m), 1.56–1.65 (2H, m), 2.22 (1H, q, J<sub>2, 3</sub> = 7.0, CH(OEt)), 9.76 (1H, t, J<sub>1, 2</sub> = 7.2, CHO); GC-MS [HP-5MS column, 5% phenylmethylsiloxane, 30 m x 0.25 mm i.d.; 60.7 kPa pressure; 70–230 °C (+10 °C/min) temperature]: t<sub>0</sub> 14.53 min (99.9%). MS of 4 (70 eV, EI) m/z: 282 (<sup>12</sup>O<sub>2</sub>), 155 (16) [M<sup>+</sup> – H]<sup>+</sup>, 137 (34), 95 (100), 81 (88), 69 (78), 55 (74), 41 (56). This aldehyde was unstable and readily gave its trimer.
(2H, dq, J 7.2, 7.2, OCH₂CHO), 3.63 (2H, dq, J 7.2, 7.2, OCH₂CHO), 4.48 [1H, t, CH(OEt)], 5.40 (1H, d, C=H), 5.80 (1H, dt, J 10.7, 7.6, C=H); GC-MS [same conditions as those for 4]: t₉ 18.85 min (91.4%). MS of 9 (70 eV, El) m/z: 263 (16) (M⁺–OEt), 233 (27), 149 (22), 119 (20), 103 (100), 93 (35), 91 (46), 85 (74), 80 (52), 75 (34), 67 (26), 57 (95), 55 (26), 41 (25). HRMS: calcd. for C₁₃H₂₀O₂–OC₂H₅, 263.2375; found, 263.2352.

(11Z,13Z)-11-Diethoxy-11,13-hexadecadiene (10). A solution of dicyclohexylborane was prepared by adding dropwise a borane-dimethyl sulfide complex (1.8 ml, d 1.287, 2.3 g, 30 mmol) to a stirred and ice-cooled solution of cyclohexene in dry THF (2M, 26 ml) in vacuo under argon. It was then concentrated (4 ml) was then added to the stirred mixture with slight evolution of hydrogen. The mixture was stirred and then for 1 h at room temperature under argon. Glacial acetic acid (4 ml) was then added to the stirred mixture with slight evolution of hydrogen. The mixture was stirred and heated at 50°C for 1 h, cooled and added to a stirred and ice-cooled solution of sodium hydroxide (12 g, 300 mmol) in water (50 ml). Subsequently, 30% hydrogen peroxide (6 ml) was added dropwise (exothermic), and stirring was continued for 10 min while ice-cooling. The mixture was diluted with water and extracted with hexane. The hexane solution was successively washed with water and brine, dried (MgSO₄), and concentrated in vacuo. The resulting residue (5.6 g) was chromatographed over SiO₂ (25 g). Elution with hexane and hexane/EtOAc (30:1) gave crude 10 (2.05 g, 76%). Further elution gave a mixture of 10 and cyclohexanol. Crude 10 contained 1 IR νmax (film) cm⁻¹: 3035 (w), C=C–H), 2927 (s), 2854 (s), 2715 (w), 1728 (s, C=O), 1599 (w, C=C), 1551 (w), 1462 (s), 1351 (m), 1242 (s, C–O), 1130 (m, C–O), 1065 (m, C–O), 1009 (m), 721 (m). This was directly employed for the next step.

(11Z,13Z)-11,13-Hexadecadienal (11). A solution of 10 (2.05 g, 6.6 mmol) in THF (30 ml) was added to a solution of oxalic acid dihydrate (3.0 g) in water (30 ml). The hydrolysis reaction was slightly exothermic. The mixture was stirred and heated for 40 min at 60°C under argon. It was then concentrated in vacuo and extracted with hexane. The hexane solution was successively washed with water, a sodium hydrogen carbonate solution and brine, dried (MgSO₄), and concentrated m vacuo. The residue (2 g) was chromatographed over SiO₂ (20 g). Elution with hexane/EtOAc (15:1) gave 1 (1.16 g, 56% based on 9, 2 steps) as a colorless oil which solidified in a deep freezer, νmax [1H, 16.33 (92.85 min (1H, J 7.6, CH₂)] 1.20–1.42 (14H, m), 1.58–1.68 (2H, m), 2.12–2.23 (2H, m), 2.41 (2H, dt, J 2.0, 7.2, CH₂CHO), 5.43 (1H, dt, J 7.7, 10.7), 5.46 (1H, dt, J 7.7, 10.7), 6.18–6.28 (2H, m), 9.76 (1H, t, J 2.0, CHO); NMR δ₁ (CDCl₃): 14.19, 20.77, 22.06, 27.43, 29.12, 29.20, 29.25, 29.29, 29.33, 29.58, 43.86, 122.86, 123.32, 131.93, 133.46, 202.67; GC-MS [same conditions as those for 4]: t₉ 16.33 [2.75%, (11Z,13E)-isomer], 16.42 [0.62%, (11E,13Z)-isomer], 15.51 min [94.45%, (11Z,13Z)-1]. MS of (11Z,13Z)-1 (70 eV, El): m/z: 236 (19) (M⁺), 109 (15), 95 (60), 82 (71), 81 (52), 68 (40), 67 (100), 55 (32), 41 (30). The other two isomers showed MS data almost identical to that of (11Z,13Z)-1. HRMS: calcd. for C₁₆H₃₀O₂, 236.2140; found, 236.2140.

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