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Improved Synthesis of (3*E*,6*Z*,9*Z*)-1,3,6,9-Nonadecatetraene, Attraction Inhibitor of Bruce Spanworm, *Operophtera bruceata,* to Pheromone Traps for Monitoring Winter Moth, *Operophtera brumata*

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The winter moth, *Operophtera brumata* (Lepidoptera: Geometridae), is an early-season defoliator that attacks a wide variety of hardwoods and, in some cases, conifers. The insect is native to Europe but has become established in at least three areas of North America including southeastern New England. The female-produced sex attractant pheromone of the winter moth was identified as (3*Z*,6*Z*,9*Z*)-1,3,6,9-nonadecatetraene (**1**), which also attracts a native congener, the Bruce spanworm, *Operophtera bruceata*. Dissection, or (for certainty) DNA molecular testing, is required to differentiate between males of the two species. Thus, a trapping method that is selective for winter moth would be desirable. A geometric isomer of the pheromone, (3*E*,6*Z*,9*Z*)-1,3,6,9-nonadecatetraene (**2**), can reportedly inhibit attraction of Bruce spanworm to traps without affecting winter moth catch, but use of the pheromone and inhibitor together has not been optimized, nor has the synthesis of the inhibitor. This paper presents two new syntheses of the inhibitor (3*E*,6*Z*,9*Z*)-1,3,6,9-nonadecatetraene based on the intermediate (3*Z*,6*Z*)-3,6-hexadecadien-1-ol (**4**), which has also been utilized in the synthesis of the pheromone. The syntheses combine traditional acetylenic chemistry and Wittig olefination reactions. In one approach, **2** was synthesized in 80% purity (20% being pheromone **1**), and in the second, tetraene **2** of 96% purity (and free of **1**) was produced in 25% overall yield from dienol **4**. The last method benefitted from a refined TEMPO-mediated PhI(OAc)$_2$ oxidation of **4** and a two-carbon homologation of the corresponding aldehyde **7**.

KEYWORDS: Winter moth; *Operophtera brumata*; Bruce spanworm; *Operophtera bruceata*; pheromone; inhibitor; synthesis; (3*E*,6*Z*,9*Z*)-1,3,6,9-nonadecatetraene

INTRODUCTION

The winter moth, *Operophtera brumata* (L.), is a common forest pest in Europe and was accidentally introduced into Canada in the 1930s (*1*). It has since spread to other parts of North America including New England. It is an occasional pest within its native range, but its impact has been severe when initially introduced into new areas. Release and establishment of exotic parasitoids can largely bring populations under control to the degree that winter moth is one of the standard examples of success in classical biological control (*2*). In New England, implementation of biological control is just beginning, and effective trapping technology would be a great aid in detecting winter moth in newly infested areas and monitoring populations. The species' female-produced sex pheromone was identified some

time ago as (3*Z*,6*Z*,9*Z*)-1,3,6,9-nonadecatetraene, **1** (*3*, *4*). This compound also attracts males of the Bruce spanworm, *Operophtera bruceata* (*3*), which occurs transcontinentally in Canada and northern United States and is very similar to the winter moth in life history, hosts, and appearance. Dissection, or molecular testing, is required to discriminate between males of the two species. Thus, a trapping method that is selective for winter moth would be potentially much more valuable than one that catches both species. Underhill et al. (*5*) reported that a geometric isomer of the pheromone, (3*E*,6*Z*,9*Z*)-1,3,6,9-nonadecatetraene (**2**), can inhibit attraction of the Bruce spanworm to traps without affecting winter moth catch. The only known synthesis of **2** (*5*) relied on (2*Z*,5*Z*,8*Z*)-2,5,8-octadecatrien-1-ol, which is not readily accessible, and we sought alternative methods to prepare this inhibitor. In our pursuit of a pheromone-based attractant for monitoring winter moth populations, we now report on two new syntheses of tetraene **2**.

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MATERIALS AND METHODS

Analytical Procedures. Gas chromatographic analyses were conducted on a Shimadzu 17A gas chromatograph (Columbia, MD) equipped with a flame ionization detector, Shimadzu AOC-20s autosampler, and AOC-20i autoinjector. The column used was a 15 m × 0.25 mm i.d., 0.25 μm, HP-5 (Agilent Technologies, Santa Clara, CA). Analyses were conducted in split mode using hydrogen as a carrier gas at 1.0 mL/min. Analyses of the pheromone **1** and the analogue **2** were also conducted on a 30 m × 0.25 mm i.d., 0.25 μm, DB-210 column (Agilent J&W). Electron-impact (EI) mass spectra were obtained at 70 eV with an Agilent Technologies 5973 mass selective detector interfaced with an Agilent 6890N GC equipped with a 30 m × 0.25 mm i.d., 0.25 μm, HP-5MS capillary column. Helium was used as the carrier gas at 1 mL/min. ^{1}H NMR spectra were obtained in CDCl$_3$ on either Bruker AV-400 MHz or Bruker AVIII-600 MHz instruments using TMS as an internal standard. Chemical shifts are reported in δ units and coupling constants in hertz. TLC analyses were conducted on Whatman AL SIL G/UV plates using 20% ethanol solution of phosphomolybdic acid and/ or UV for visualization of spots. Flash chromatography was carried out with 230−400 mesh silica gel (Fisher Scientific, Fair Lawn, NJ).

Chemicals and Supplies. Unless otherwise specified, all reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI). Lindlar catalyst, 5% Pd on CaCO$_3$, lead poisoned, was purchased from Strem Chemicals (Newburyport, MA). Reactions were carried out under N$_2$ in oven-dried glassware. Sodium sulfate was used to dry reaction mixtures. Anhydrous tetrahydrofuran (THF) and ether were obtained by distillation from sodium benzophenone ketyl, and methylene chloride was distilled from calcium hydride. 3-Butyn-1-ol was protected as a tetrahydro-pyranyl ether in the presence of pyridinium *p*-toluenesulfonate (*6*) instead of hydrochloric acid (*7*). The resultant ether was isolated by distillation (bp 50 °C/3 mmHg) in 75% yield and 94% purity. The tosylate of 2-dodecyn-1-ol (Advanced Synthesis Technologies, San Ysidro, CA) was prepared using tosyl chloride and powdered KOH in ether and was sufficiently pure (a single spot on TLC) to be used in the alkylation step (*8*) (see below) without further purification.

3,6-Hexadecadiyn-1-ol (3). To a solution of 1-(tetrahydo-2*H*-pyran-2-yloxy)-3-butyne (17.40 g, 0.11 mol) in dry THF (90 mL) was added a solution of ethylmagnesium bromide in ether (39 mL of 3 M; 0.12 mol), maintaining the temperature at ∼0 °C. The resulting mixture was warmed in a water bath (30 °C) until ethane evolution ceased (15−20 min). The solution was cooled to ∼0 °C, and cuprous bromide (649 mg, 2.262 mmol) was added at once. After 15 min of stirring, a solution of crude of 2-dodecyn-1-yl tosylate (34.30 g, 0.10 mol) in THF (60 mL) was added, maintaining the temperature at 0−5 °C. The mixture was stirred at that temperature for 30 min, allowed to warm to 25 °C, stirred for an additional 45 min, and then poured into a cold, saturated solution of ammonium chloride. The organic material was extracted with ether (3 × 100 mL), and the combined ether extract was washed twice with a NH$_4$Cl solution and dried. After evaporation of the solvent, the remainder was dissolved in methanol (100 mL) containing pyridinium *p*-toluenesulfonate (2.5 g) and heated at 50−60 °C until complete deprotection was achieved. The mixture was concentrated on a rotary evaporator, taken into hexanes/ether, 1:1, washed with water, and dried. Concentration of the extract furnished crude alcohol (28.29 g), which was purified in small batches by flash chromatography with hexanes/ethyl acetate, 3:2, to provide **3** (yield 80%, 99% pure by GC): ^{1}H NMR (400 MHz) 0.89 (t, *J* = 7.0, 3H), 1.27 (m, 12H), 1.49 (tt, *J* = 7.5,

2H), 2.06 (OH), 2.16 (tt, *J* = 7.2, 2.8), 2,46 (m, 2H), 3.15 (tt, *J* = 2.4, 2H), 3.72 (t, *J* = 6.2, 2H). The data are in good agreement with those reported in the literature (*9*, *10*).

(3*Z*,6*Z*)-3,6-Hexadecadien-1-ol (4). 3,6-Hexadecadiyn-1-ol (**3**) (13.69 g, 58.50 mmol) was dissolved in a mixture of methanol (490 mL), cyclohexene (25 mL), and quinoline (1.89 mL) and stirred in the presence of 5% Pd on CaCO$_3$ (1.37 g) in a hydrogen atmosphere. After about 8 h, the rate of hydrogen consumption dropped from 4.70 to 0.23 mL/min, and GC analysis showed almost no starting material present. The mixture was filtered through a short pad of Celite, the pad was rinsed with MeOH (50 mL), and the filtrate was concentrated and taken into ether/ hexanes, 1:1 (150 mL). The organic extract was washed with 5% HCl and brine and then was dried and concentrated. Flash chromatography with hexanes/ethyl acetate, 4:1, gave dienol **4** (12.41 g, yield 89%, purity 97% by GC on DB-5 column): GC-MS (*m/z*, %) 238 (3, M$^+$), 220 (2, M$^+$ − H$_2$O), 152 (4), 135 (9), 121 (17), 107 (21), 93 (52), 79 (100), 67 (62), 55 (38); ^{1}H NMR (400 MHz) 0.89 (t, *J* = 6.8, 3H), 1.25−1.37 (m, 14H), 1.52 (OH), 2.06 (br dt, *J* ∼ 7.0, 2H), 2.38 (br dt, *J* ∼ 7.0, 2H), 2.83 (dd, *J* = 7.2, 2H), 3.67 (t, *J* = 6.4, 2H), 5.24−5.45 (m, 3H), 5.55 (dtt, *J* = 11.2, 7.6, 1.6, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) 14.34, 22.91, 25.97, 27.50, 29.54, 29.56, 29.78, 29.82, 29.85, 31.02, 32.13, 62.48, 125.53, 127.57, 130.89, 131.83. Mass spectrometric and NMR data are in a close agreement with literature values (*9*). Mass spectra of two minor impurities (total 3%) showed ions at *m/z* 222, apparently arising from a loss of H$_2$O from molecular ions of corresponding monoenic alcohols.

(3*Z*,6*Z*)-3,6-Hexadecadienyltriphenylphosphonium bromide (5) was prepared following a published procedure (*11*). Dienol **4** was first converted to (3*Z*,6*Z*)-1-bromo-3,6-hexadecadiene using tri-phenylphosphine dibromide and imidazole (yield 88%), and then the bromide reacted with triphenylphosphine in acetonitrile (yield 92%).

(3*Z*,6*Z*,9*Z*)-1,3,6,9-Nonadecatetraene (1). A *cis*-olefination procedure by Bestmann et al. (*4*), reacting acrolein with a phos-phorane generated from bromide **5** using sodium bis(trimethyl-silyl)amide at −75 °C was followed. The pheromone **1** at 95% purity was isolated in 68% yield: GC-MS (*m/z*, %) 260 (5, M$^+$), 219 (5), 206 (15), 147 (7), 133 (14), 119 (28), 106 (39), 91 (95), 80 (90), 79 (100), 67 (44), 55 (23), 43 (24), 41 (44) [data are consistent with those previously reported (*4*)]; ^{1}H NMR (400 MHz) 0.89 (t, *J* = 6.8, 3H), 1.20−1.40 (m, 14H), 2.06 (br dt, *J* ∼ 7.0, 2H), 2.82 (br dd, *J* ∼ 6.8, 2H), 2.98 (dd, *J* = 6.4, 2H), 5.13 (br d, *J* = 10.0, 1H), 5.22 (dd, *J* = 17.0, 2.0, 1H), 5.39 (m, 5H), 6.03 (br dd, *J* ∼ 10.8, 1H), 6.68 (dddd, *J* = 17.0, 10.8, 10.0, 1.2, 1H); ^{13}C NMR 14.34, 22.91, 25.88, 26.31, 27.50, 29.56 (two C), 29.79, 29.83, 29.88, 32.14, 117.62, 127.55, 127.63, 129.17, 129.53, 130.67, 130.80, 132.20. NMR data are in close agreement with those previously reported (*9*, *11*, *12*).

Wittig Trans-olefination of Acrolein with Salt 5. Butyllithium (820 μL of 2.5 M in hexanes; 2.05 mmol) was added to the suspension of phosphonium salt **5** (1.182 g, 2.1 mmol) in THF/ ether mixture (4 mL + 3 mL) at −70 °C. The dark brown solution was stirred at this temperature for 20 min, then a solution of acrolein (138 μL, 2.06 mmol) in ether (150 μL) was added, and the mixture was stirred for another 30 min. The resulting light yellow suspension was treated slowly with a second equivalent of BuLi (820 μL of 2.5 M) at −73 °C, upon which a dark brown color was restored. After 20 min of stirring, the reaction mixture was slowly quenched with HCl (543 μL of 3.77 M in ether; 2.05 mmol), maintaining the temperature below −70 °C. The cooling bath was removed, and the mixture was diluted with THF (20 mL), stirred at 25 °C for 5 h, and then poured into saturated NH$_4$Cl solution. The mixture was extracted with hexanes (3 × 20 mL), and the

combined organic extracts were washed with water, dried, and concentrated. The residue was flash chromatographed with hexanes to give the olefination product (300 mg, 57%) as a 4:1 mixture of **2** and **1** as determined by GC analysis on DB-210 capillary column. Repeating the above procedure while adding the second equivalent of BuLi at −30 to −40 °C gave **2**/**1** in a 51:49 ratio.

Methyl (2*E*,5*Z*,8*Z*)-2,5,8-Octadecatrienoate (6). *Method A: CrO₃·Py.* Dried over P₂O₅, freshly powdered chromium(VI) oxide (600 mg, 6 mmol) was added to a solution of dry pyridine (970 μL, 12 mmol) in dichloromethane (13 mL) at 0−5 °C. The mixture was slowly warmed to room temperature and stirred for an additional 30 min. Dienol **3** (238 mg, 1 mmol), dissolved in dichloromethane (1 mL), was added slowly at 20 °C. After 1.5 h, anhydrous ether (20 mL) was added, and the resulting mixture was filtered through a pad of anhydrous MgSO₄. The precipitate was thoroughly washed with an additional amount of dry ether (50 mL), and washings were combined. The solvent was evaporated, and the residue was dissolved in CH₂Cl₂ (5 mL) and added to a solution of methyl (triphenylphosphoranylidene)acetate (501 mg, 1.5 mmol) in CH₂Cl₂ (15 mL) at 22 °C. After 2 h, or when the TLC (CH₂Cl₂) showed no intermediate aldehyde **7** present, the mixture was concentrated and chromatographed with hexanes/ CH₂Cl₂, 2:3, to yield 35 mg of a mixture containing 64% of the 2*Z* isomer (see Method B) and 23% of the desired ester **6** and 126 mg of a product containing 88% ester **6**. The second fraction was chromatographed on 15% AgNO₃ on SiO₂ with hexanes/ ethyl acetate, 10:1, to give 113 mg (39%) **6** at 96% purity: GC-MS (*m/z*, %) 292 (M⁺ 3), 261 (3), 238 (16), 139 (71), 119 (26), 111 (32), 91 (48), 79 (100), 67 (69), 55 (44), 41 (49); ¹H NMR (600 MHz) 0.89 (t, *J* = 6.8, 3H), 1.27 (m, 12H), 1.33 (m, 2H), 2.04 (br dt, *J* = 7.2, 2H, H-10), 2.78 (br dd, *J* = 7.2, 2H), 2.98 (br dd, *J* = 7.2, 2H), 3.73 (s, 3H, OCH₃), 5.32 (m, 1H), 5.41 (m, 2H), 5.58 (m, 1H), 5.86 (dt, *J* = 15.9, 3.1, 1H, H-2), 6.97 (dt, *J* = 15.9, 7.3, 1H, H-3); ¹³C NMR (CDCl₃, 151 MHz) 14.28, 22.89, 25.86, 27.52, 29.54 (two C), 29.77, 29.82, 29.84, 30.20, 51.58, 121.45, 124.53, 127.21, 131.10, 131.37, 147.39, 167.26. Anal. Calcd for C₁₉H₃₂O₂: C, 78.02; H, 11.05. Found: C, 78.08; H, 11.10.

Method B: PhI(AcO)₂/TEMPO. (Diacetoxyiodo)benzene (818 mg, 2.54 mmol) was added to a stirred solution of **4** (550 mg, 2.31 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, 36 mg, 0.23 mmol) in a mixture of pentane (2 mL) and dichloromethane (3 mL). The mixture was stirred at 25 °C for 35 min (upon which the reaction was over by TLC), diluted with CH₂Cl₂ (15 mL), and washed with a saturated Na₂S₂O₃ solution (12 mL), and the aqueous layer was extracted with CH₂Cl₂ (4 × 5 mL). The combined organic extracts were cooled to 0 °C, washed with a saturated NaHCO₃ solution to pH 8 and then with a brine solution, and dried for 2 h. After evaporation of the solvent, the crude aldehyde **7** was added to the solution of methyl (triphenylphosphoranylidene)acetate (1.132 g, 3.39 mmol) in CH₂Cl₂ (22 mL) at 25 °C and stirred for 1.5 h, or until the reaction had gone to completion as observed by TLC. The solvent was evaporated, and the residue was subjected to flash chromatography with hexanes/CH₂Cl₂, 1:1, to give two fractions. The first fraction (27 mg) contained a cis-olefination product and an unknown compound (*R*ᶠ 0.47 and 0.41, respectively; hexanes/ CH₂Cl₂, 1:1), and the second fraction consisted of 96% pure ester **6** (412 mg, 60%, *R*ᶠ 0.34). The subsequent chromatography of the first fraction with hexanes/CH₂Cl₂, 2:1, gave methyl (2*Z*,5*Z*,8*Z*)-2,5,8-octadecatrienoate (10 mg) of 95% purity: GC-MS (*m/z*, %) 292 (M⁺ 9), 232 (5), 233 (5), 226 (5), 193 (6), 126 (31), 105 (48), 111 (36), 91 (69), 79 (87), 67 (100), 55 (48), 41 (56); ¹H NMR (600 MHz, CDCl₃) 0.89 (t, *J* = 6.8, 3H), 1.28 (m, 12H), 1.34 (m, 2H), 2.05 (br dt, *J* = 7.2, 2H, H-10), 2.84 (br dd, *J* = 7.2, 2H),

3.47 (br dd, *J* = 7.2, 2H), 3.73 (s, 3H, OCH₃), 5.33 (m, 1H), 5.37−5.44 (m, 3H), 5.80 (dt, *J* = 11.7, 3.2, 1H, H-2), 6.19 (dt, *J* = 11.7, 7.5, 1H, H-3); ¹³C NMR (CDCl₃, 151 MHz) 14.29, 22.89, 25.99, 27.50, 27.75, 29.55 (two C), 29.79, 29.83, 29.89, 32.14, 51.23, 119.42, 126.16, 127.54, 130.56, 130.93, 148.39, 166.92. Anal. Calcd for C₁₉H₃₂O₂: C, 78.02; H, 11.05. Found: C, 77.63; H, 11.09.

(2*E*,5*Z*,8*Z*)-2,5,8-Octadecatrien-1-ol (8). To a stirred solution of ester **6** (392 mg, 1.34 mmol) in anhydrous CH₂Cl₂ (8 mL) was added diisobutylaluminum hydride (2.8 mL of 1.0 M in hexanes, 2.8 mmol) at −70 °C. After 30 min, the reaction was observed to have gone to completion by TLC (hexanes/ethyl acetate, 3:1). The reaction mixture was diluted with hexanes/ether, 3:1 (60 mL), then quenched with a saturated NH₄Cl solution (17 mL) at −35 °C and allowed to warm to room temperature. After additional stirring for 20 min, the solid was filtered, the layers were separated, the aqueous layer was extracted with hexanes/ ether, 1:1 (50 mL), and the combined organic extracts were washed with saturated NH₄Cl, brine, and then dried. The solution was concentrated and chromatographed with hexanes/ethyl acetate, 4:1, to yield alcohol **8** (300 mg, 85%) of 93% purity: GC-MS (*m/z*, %) 246 (M⁺ − H₂O, 12), 192 (4), 133 (13), 119 (25), 105 (53), 91 (72), 79 (100), 67 (75), 55 (48), 41 (60); ¹H NMR (600 MHz) 0.89 (t, *J* = 6.8, 3H), 1.27 (m, 12H), 1.34 (m, 2H), 2.04 (br dt, *J* ∼ 7.0, 2H, H-10), 2.79 (br dd, *J* ∼ 7.0, 2H), 2.83 (br dd, *J* ∼ 7.0, 2H), 4.11 (m, 2H), 5.33 (m, 1H), 5.42 (m, 3H), 5.68 (dt, *J* = 15.6, 6.2, 1H), 5.71 (dt, *J* = 15.6, 6.2, 1H); ¹³C NMR (CDCl₃, 151 MHz) 14.31, 22.89, 25.81, 27.49, 29.55 (two C), 29.78, 29.82, 29.86, 30.22, 32.13, 63.91, 127.02, 127.67, 129.64 (two C), 130.77, 131.32. Anal. Calcd for C₁₈H₃₂O: C, 81.73; H, 12.22. Found: C, 81.53; H, 12.01.

(2*E*,5*Z*,8*Z*)-2,5,8-Octadecatrienal (9). A mixture of (2*E*,5*Z*, 8*Z*)-2,5,8-octadecatrien-1-ol (290 mg, 1.09 mmol) and Dess− Martin periodinane (933 mg, 2.20 mmol) in CH₂Cl₂ (20 mL) was stirred for 1 h at 25 °C. A solution of Na₂S₂O₃ (3.6 g) in water (20 mL) was added, the mixture was stirred for 10 min, and then cooled to 0−5 °C and treated with a saturated NaHCO₃ solution (35 mL). The stirring was continued for 10 min, the layers were separated, the aqueous layer was extracted with ether/hexanes, 1:1 (50 mL), and combined organic extracts were washed with water and dried. Evaporation of the solvent and flash chromatography of the residue with hexanes/ethyl acetate, 9:1, afforded aldehyde **9** (238 mg, 83%), which was unstable under GC conditions: GC-MS (*m/z*, %) 262 (M⁺ 3), 218 (5), 208 (10), 149 (6), 135 (15), 121 (33), 109 (62), 96 (44), 95 (42), 93 (46), 92 (36), 91 (52), 81 (94), 80 (48), 79 (100), 69 (30), 67 (86), 57 (28), 55 (55), 43 (43); ¹H NMR (600 MHz) 0.89 (t, *J* = 6.8, 3H), 1.27 (m, 12H), 1.35 (m, 2H), 2.04 (br dt, *J* = 7.5, 2H, H-10), 2.80 (br dd, *J* = 7.5, 2H), 3.12 (br dd, *J* = 7.5, 2H), 5.41 (dtt, *J* = 11.0, 7.3, 1.5, 1H), 5.43 (m, 2H), 5.59 (dtt, *J* = 11.0, 7.3, 1.5, 1H), 6.17 (ddt, *J* = 15.6, 7.8, 1.5, 1H, H-2), 6.85 (dt, *J* = 15.6, 6.3, 1H, H-3), 9.53 (d, *J* = 7.8,1H, H-1); ¹³C NMR (CDCl₃, 151 MHz) 14.31, 22.89, 25.87, 27.52, 29.54 (two C), 29.76, 29.80 (two C), 30.74, 32.12, 123.79, 126.93, 131.25, 131.99, 133.25, 156.41, 194.02. ¹H NMR data match those reported in the literature (5).

(3*E*,6*Z*,9*Z*)-1,3,6,9-Nonadecatetraene (2). A procedure by Underhill et al. (5) was followed. Wittig reaction of aldehyde **9** (228 mg, 0.87 mmol) with a phosphorane generated from methyl-triphenylphosphonium iodide (389 mg, 0.96 mmol) and BuLi (348 μL of 2.5 M in hexanes, 0.87 mmol) gave a crude condensation product that was purified by flash chromatography with hexanes to yield 136 mg (60%) of **2** in 96% purity by GC. GC-MS (*m/z*, %) 260 (4, M⁺), 219 (4), 206 (15), 147 (7), 133 (14), 119 (25), 106 (45), 93 (41), 91 (100), 80 (84), 79 (96), 67 (45), 55 (24), 43 (24), 41 (44); ¹H NMR (600 MHz) 0.89 (t, *J* = 6.8, 3H), 1.28 (m, 12H),
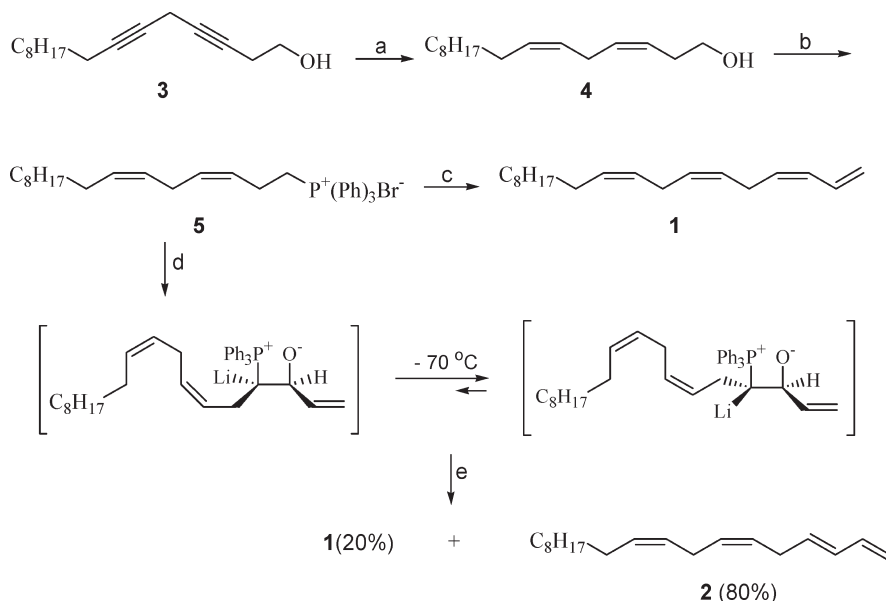
Figure 1. Synthesis of (3Z,6Z,9Z)-1,3,6,9-nonadecatetraene (**1**) and (E,Z,Z)-1,3,6,9-nonadecatetraene (**2**) via Wittig cis- and trans-olefinations. Reagents and conditions: (a) H₂/Pd-CaCO₃/cyclohexene/quinoline/MeOH; (b) 1, Ph₃PBr₂/imidazole; 2, Ph₃P; (c) 1, [(CH₃)₃Si]₂NNa/THF, −75 °C; 2, CH₂=CHCHO; (d) 1, BuLi, −70 °C; 2, CH₂=CHCHO; 3, BuLi, −70 °C; (e) H⁺/THF, −70 °C to room temperature.

1.35 (m, 2H), 2.06 (br dt, J = 7.2, 2H), 2.80 (br dd, J = 7.2, 2H), 2.88 (br dd, J = 7.0, 2H), 4.98 (br d, J = 10.2, 1H), 5.12 (br d, J = 16.7, 1H), 5.35 (m, 1H), 5.43 (m, 3H), 5.70 (dt, J = 15.6, 6.7, 1H, H-4), 6.09 (br dd, $J \sim$ 15.6, 10.6, 1H, H-3), 6.33 (ddd, J = 16.7, 10.5, 1H, H-2); ^{13}C NMR (151 MHz, CDCl₃) 14.32, 22.90, 25.83, 27.49, 29.56 (two C), 29.79, 29.83, 29.88, 30.52, 32.14, 115.37, 126.95, 127.68, 129.63, 130.77, 131.44, 133.18, 137.33. ^{1}H NMR data are in a close agreement with those reported (*5*).

(2E,6Z)-2,6-Hexadecadienal (10). The oxidation of dienol **4** (238 mg, 1 mmol) with PhI(OAc)₂ (354 mg, 1.1 mmol) and TEMPO (15 mg) in a mixture of pentane and dichloromethane (0.8 mL + 1.2 mL) was conducted as described above. The crude aldehyde **7** was dissolved in dichloromethane (3 mL) and added to a solution of (triphenylphosphoranylidene)acetaldehyde (365 mg, 1.2 mmol) in dichloromethane (15 mL). The mixture was stirred at 20 °C for 40 h and then concentrated and chromatographed with CH₂Cl₂/hexanes, 2:1, to give (2E,6Z)-2,6-hexadecadienal (115 mg, 49%) in 95% purity: GC-MS (m/z, %) 236 (M⁺, 2), 192 (2), 166 (11), 138 (3), 123 (7), 111 (16), 97 (31), 83 (39), 70 (100), 69 (48), 68 (11), 67 (26), 57 (22), 55 (59), 54 (13), 43 (31), 41 (49); GC-MS (CI, MH₃) 254 (M⁺ + 18); ^{1}H NMR (600 MHz) 0.89 (t, J = 6.8, 3H), 1.29 (m, 12H), 1.33 (m, 2H), 2.03 (br dt, J = 7.5, 2H), 2.27 (br dt, J = 7.5, 2H), 2.40 (br dt, J = 7.5, 2H), 5.33 (m, 1H), 5.45 (m, 1H), 6.15 (dd, J = 7.8, 15.7, 1H, H-2), 6.85 (dt, J = 15.7, 6.8, 1H, H-3), 9.50 (d, J = 7.8, 1H, H-1) [data are in close agreement with literature values (*13*)]; ^{13}C NMR (CDCl₃, 151 MHz) 14.30, 22.88, 25.79, 27.53, 29.53 (two C), 29.75, 29.80 (two C), 31.11, 32.96, 127.48, 132.03, 133.46, 158.20, 194.18.

RESULTS AND DISCUSSION

Reports on synthesis of the winter moth pheromone **1** are plentiful (*3, 4, 9, 11, 12, 14−16*), including methods utilizing dienol **4** as a main building block (*3, 4, 9, 11*). Because dienol **4** could be expediently prepared in two steps from commercially available starting materials, we also chose this intermediate to synthesize pheromone **1** for field trials (**Figure 1**). We basically followed a route converting **4** to the corresponding bromide (*11*) and further to the phosphonium salt **5**, then conducting cis-Wittig olefination as described (*4, 11*).

An obvious (and convenient) way of making the isomeric tertraene **2** would have been to utilize the same phosphonium salt **5** in a Wittig trans-olefination (a Schlosser modification) with acrolein (*17, 18*). Although this technique provides an excellent trans-stereoselectivity (>96%) with nonstabilized ylides and both aliphatic and aromatic aldehydes, it has been largely overlooked in synthetic chemistry. This procedure was previously successfully used (*19*) for trans-olefination of (E)-4,4-dimethoxy-2-butenal to synthesize stink bug pheromone analogues. The essence of the Schlosser modification of the Wittig reaction is in applying a second equivalent of base after the addition of an aldehyde to a phosphorane, upon which a deprotonation of the betaine−LiBr adduct (**Figure 1**) occurs and a fast equilibrium between erythro and threo intermediates takes place (*18*). It has been shown that at −30 °C the equilibrium was predominantly shifted to a sterically less hindered threo isomer resulting after acidification almost entirely in trans-olefins (*17−19*).

We conducted the olefination by generating an ylide from salt **5** at −70 °C using butyl lithium, then added acrolein, followed by the second equivalent of BuLi, and then let the temperature warm to −40 to −30 °C. Quenching the reaction mixture with HCl resulted in a 51:49 ratio of **2** and **1**, found by a GC analysis of the reaction product on a DB-210 column (*5*). Maintaining the reaction temperature at −70 °C throughout the entire process allowed the improvement of the ratio of isomers **2** and **1** to 80:20, but also indicated that a complete thermodynamic control leading to trans-olefin **2** could hardly be achieved even at very low temperatures. In an attempt to conduct the reaction at −100 °C, we ran into technical difficulties, such as insolubility of intermediates in the reaction medium. It was still possible to isolate pure **2** from a 80:20 mixture by HPLC chromatography on a Ag⁺−SiO₂ column (*5*), but we sought a more convenient route.

An alternative path to tetraene **2** entailed oxidation of dienol **4** to aldehyde **7** with a subsequent two-carbon homologation and, finally, one-carbon Wittig elongation (**Figure 2**). The first step in this process was, in fact, described in the syntheses of pheromone **1** (*3, 9*) and (3Z,6Z,9Z)-3,6,9-nonadecatetraene, a pheromone component of *Peribatodes rhomboidaria* (*20*). Homologous (3Z,6Z)-3,6-octadecadienal has also been similarly employed in the synthesis of (3Z,6Z,9Z)-1,3,6,9-heneicosatetraene, a sex
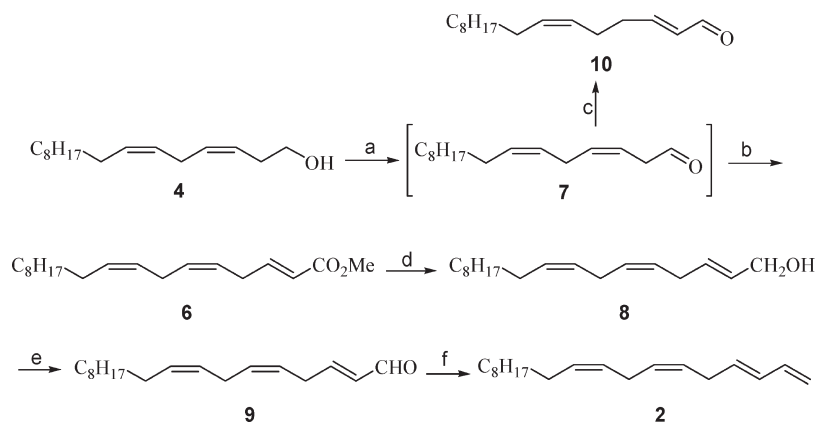
Figure 2. Synthesis of (3*E*,6*Z*,9*Z*)-1,3,6,9-nonadecatetraene (**2**) via Wittig olefination with stabilized ylide. Reagents and conditions: (a) PhI(AcO)$_2$-TEMPO/CH$_2$Cl$_2$, room temperature; (b) Ph$_3$P=CHCO$_2$Me/CH$_2$Cl$_2$, room temperature; (c) Ph$_3$P=CHCHO/CH$_2$Cl$_2$; (d) DIBAL-H/CH$_2$Cl$_2$, −70 °C; (e) Dess−Martin periodinane; (f) Ph$_3$P$^+$CH$_3$I$^-$-BuLi/THF, 0 °C.

pheromone of the arctiid moth, *Utetheisa ornatrix* (*7*). In these papers, a labile aldehyde **7** (or its C-18 homologue) was prepared by oxidation of corresponding alcohols with a 6-fold excess of the chromium(VI) oxide−dipyridine (*21*) and without purification olefinated in a Wittig reaction in low to moderate (∼50%) yields (*7, 9, 20*). Following this protocol, we ran CrO$_3$·Py oxidation of **4** (97% pure) with a subsequent olefination of crude **7** with methyl (triphenylphosphoranylidene)acetate at room temperature in CH$_2$Cl$_2$ and obtained a product showing a single spot on TLC but having only 88% purity by GC. Argentation chromatography of this material afforded 96% pure ester **6** in 39% yield. Aside from the facts of a low yield, a large excess of CrO$_3$·Py, and using argentation chromatography for purification, hexavalent chromium is extremely toxic and a tightly regulated product in the chemical industry. Hence, we sought a more suitable oxidation reagent. (Diacetoxyiodo)benzene in combination with a catalytic amount of TEMPO was described in the literature as a mild and selective reagent for oxidation of alcohols to aldehydes (*22*), including an example of a homoallylic alcohol with a 3*Z* double bond (*23*). We found that with only 20% excess of PhI(OAc)$_2$, the oxidation of **4**, followed by olefination of crude aldehyde with Ph$_3$P=CHCOOMe, provided ester **6** in a 60% yield and 96% chemical purity after conventional flash chromatography. A small amount of cis-olefination product was cleanly separated from ester **6**, thus ensuring that the final tetraene will not contain pheromone **1**. Hence, (diacetoxyiodo)benzene/TEMPO oxidation is clearly advantageous over CrO$_3$·Py in a two-step conversion of dienol **4** to the trienic ester **6**. Further transformation of ester **6** to the desired tetraene **2** was accomplished by a traditional route (**Figure 2**) that entailed a low-temperature diisobutylaluminum hydride reduction (*24*), a Dess−Martin periodinane oxidation (*25*) of alcohol **8**, and, finally, a Wittig olefination of aldehyde **9** (*5*). Overall yield of the tetraene **2** from dienol **4** was 25% and the chemical and isomeric purity 96%, as judged from a GC-MS analysis. Two small impurities displayed in their mass spectra ions at *m/z* 260, corresponding to the molecular ion of **2**.

Next, we sought to shorten the three-step homologation of aldehyde **7**. (Triphenylphosphoranylidene)acetaldehyde is a stable commercially available phosphorane that was used for a direct two-carbon trans-homologation of both aromatic and aliphatic aldehydes (*26*). Normally, the reaction with this stabilized ylide requires heating in benzene (*26*), but could also be accomplished at room temperature in CH$_2$Cl$_2$ (*27*). However, stirring of aldehyde **7** with (triphenylphosphoranylidene)-acetaldehyde in CH$_2$Cl$_2$ at 20 °C and/or in benzene at 80 °C,

instead of producing a Wittig condensation, unexpectedly resulted in aldehyde **10**, by means of isomerizing the 3*Z* double bond in the starting aldehyde to the 2*E* position. We are unaware of any other example of a homoallylic alcohol in such a reaction, but it seems that aldehyde **7** and Ph$_3$P=CHCHO reversibly form a betaine adduct that is basic enough to promote a prototropic isomerization before collapsing back to starting materials. Interestingly, we did not notice any isomerization when conducting Wittig reaction of **7** with Ph$_3$P=CHCOOMe under similar conditions. Other attempts to shorten a three-step homologation sequence were not productive either. Although the Wittig reaction of aldehyde **7** with (triphenylphosphoranylidene)acetonitrile was successful (unpublished results), DIBAL-H reduction of the resultant nitrile, followed by acidic hydrolysis of an intermediate imine, provided a low yield of aldehyde **9**.

In summary, we developed two new syntheses of the tetraene **2** from dienol **4**. In the first approach, Wittig trans-olefination with a nonstabilized ylide obtained from salt **5** was not completely stereoselective, thus affording a 4:1 mixture of inhibitor **2** and pheromone **1**. This method might have a practical utilization, provided the content of **2** in the mixture is high enough to shut down trap captures of Bruce spanworm. The second, more advanced, route benefitted from an improved oxidation of **4** and subsequent two-carbon homologation of the aldehyde **7** and furnished tetraene **2** not contaminated with **1**.

Field trials with different blends of tetraenes **1** and **2** were conducted in November and December 2008 on the grounds of the Massachusetts National Cemetery, Bourne, MA, against winter moth and in November 2008 in Cadwell State Forest, Massachusetts, against a Bruce spanworm population. Briefly, tetraene **1** was indeed attractive to winter moth and Bruce spanworm males, whereas the isomer **2** was inactive against both species as reported (*5, 28*). Tetraene **2** did show an inhibitory effect against Bruce spanworm when added to pheromone **1** (*5, 28*), but it surprisingly did so against winter moth population as well. In a separate paper, we will demonstrate how the trap design and placement of the pheromone and the inhibitor dispensers affect trap catches.

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