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Direct Aldehyde Homologation Utilized To Construct a Conjugated-Tetraene Hydrocarbon Insect Pheromone

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New phosphonate reagents were developed for the two-carbon homologation of aldehydes to methyl- or ethyl-branched unsaturated aldehydes and used in the practical synthesis of (2*E*,4*E*,6*E*,8*E*)-3,5-dimethyl-7-ethyl-2,4,6,8-undecatetraene (**1**), a pheromone of the beetle *Carpophilus lugubris*. The phosphonate reagents, diethyl ethylformyl-2-phosphonate dimethylhydrazone and diethyl 1-propylformyl-2-phosphonate dimethylhydrazone, contained a protected aldehyde group instead of the usual ester group. A homologation cycle entailed condensation of the reagent with the starting aldehyde, followed by removal of the dimethylhydrazone protective group with a biphasic mixture of dilute HCl and petroleum ether. This robust two-step process replaces the standard three-step aldehyde homologation route using ester-based Horner−Wadsworth−Emmons reagents. The new synthesis of compound **1** from (2*E*)-2-methyl-2-butenal was run on a 10-g scale and required just five steps (two cycles of condensation and deprotection, followed by a final Wittig olefination) instead of the usual seven. In addition, the Wittig olefination step was simplified and its *E*-isomer selectivity was improved. The overall yield for the entire synthetic pathway was increased from 20% to 37%, enhancing the commercial potential of *Carpophilus* pheromones.

KEYWORDS: Aldehyde homologation; diethyl ethylformyl-2-phosphonate dimethylhydrazone; diethyl 1-propylformyl-2-phosphonate dimethylhydrazone; sap beetle; *Carpophilus lugubris*; Nitidulidae

INTRODUCTION

A recurring theme in the synthesis of various polyketide natural products and other compounds is two-carbon homologation of aldehydes to α-alkyl-α,β-unsaturated aldehydes. A typical approach based on the Horner−Wadsworth−Emmons condensation (*1*) uses a phosphonate ester and involves three synthetic steps: The phosphonate condensation step extends the chain by two carbons while introducing an (*E*) double bond, an α-alkyl branch (size depending on the choice of phosphonate reagent), and a terminal ester group. The ester is then reduced to an α,β-unsaturated alcohol, and the alcohol is partially oxidized to the desired α,β-unsaturated aldehyde. One way to shorten this scheme would be to use a homologating reagent that keeps the oxidation state of an aldehyde throughout.

A variety of options were considered. Aldehyde Wittig reagents such as α-formylethylidenetriphenylphosphorane are known (*2*, *3*), but in our hands the reagent was not reactive toward α,β-branched unsaturated aldehydes, such as (2*E*)-2-methyl-2-butenal (R.J.P., unpublished results). Phosphonate anions are generally more reactive toward aldehydes than the analogous phosphoranes (*4*). Aldehyde phosphonates (where the ester group is replaced by an aldehyde) can be readily prepared (*5*), but using them directly in Wittig−Horner reactions is not practicable because of self-condensation. Reactions with aldehyde phosphonates protected as imines and acetals have been reported, but these reagents also have problems with side reactions, insufficient reactivity, and lability of reagents or products (*4*, *6*). The silylaldimines are the functional equivalents of protected aldehyde phosphonates and have been used in Horner−Wadsworth−Emmons-like reactions (*7*, *8*); however, reaction conditions to form and use silylaldimines are not operationally convenient (*8*), and we chose to further explore phosphonate chemistry.

Protection of carbonyl compounds as dimethylhydrazones is a common practice, and the incorporation and removal of this group have been studied extensively (*9*−*11*). However, to our knowledge, the use of aldehyde phosphonates protected as dimethylhydrazones in Horner−Wadsworth−Emmons-type reactions had not been exploited previously. The dimethylhydrazone phosphonates were prepared without difficulty, were stable enough to be distilled, and readily entered condensation reactions; subsequent removal of the dimethylhydrazone protective group could be easily accomplished, even for delicate product aldehydes. Using these reagents led to a two-step homologation cycle (condensation and deprotection), instead of the previous three-step cycle.

Here, the new approach was applied to the preparation of pheromones for *Carpophilus* sap beetles (Coleoptera: Nitidul-

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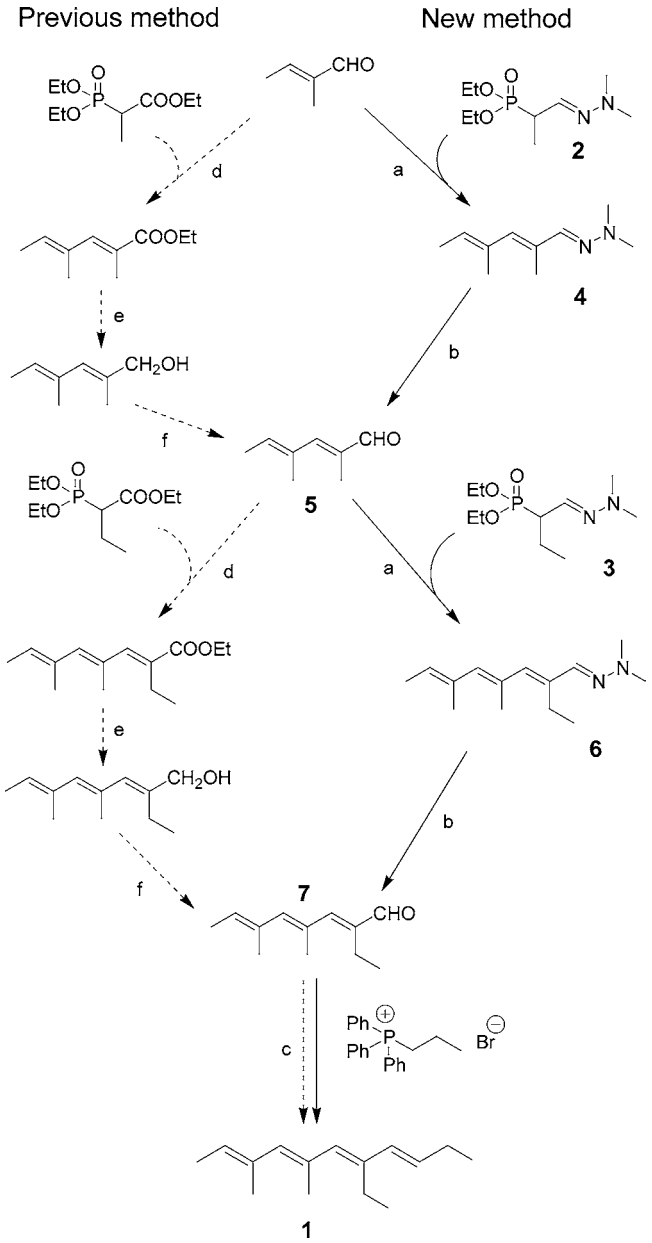
Scheme 1. Comparison of Synthetic Pathways to Compound **1** via Ester-Based Phosphonate Reagents (Previous Method) and Protected-Aldehyde-Based Phosphonate Reagents (New Method)[a]



[a] Reaction conditions: (a) phosphonate **2** or **3**, LiN(*i*Pr)$_2$, THF, 25 °C, 20 h; (b) dilute HCl and petroleum ether, 25 °C, 4 h for **5** and 17 h for **7**; (c) $[Ph_3PCH_2CH_2CH_3]^+Br^-$, *n*-BuLi, THF, <10 °C, then 25 °C for 1.5 h; (d) triethyl-2-phosphonopropionate or triethyl-2-phosphonobutyrate, *n*-BuLi, THF, <10 °C, then 25 °C for 2 h; (e) $LiAlH_4$, Et_2O, <15 °C, then 25 °C for 4 h; (f) MnO_2, CH_2Cl_2, 25 °C, 4 h.

idae). These beetles, worldwide pests of a variety of fruits and grains, have male-produced aggregation pheromones consisting of conjugated triene and tetraene hydrocarbons, which are attractive to both sexes (*12*). One species, the dusky sap beetle, *Carpophilus lugubris* Murray, uses (2*E*,4*E*,6*E*,8*E*)-3,5-dimethyl-7-ethyl-2,4,6,8-undecatetraene (**1**) as its major pheromone component (**Scheme 1**) (*13*). Tetraene **1** provided a rather challenging test for the new synthetic method because it is relatively labile and because the ethyl branch at the C7-position can lead to unwanted geometrical isomers and a rather poor overall yield (*14*). By use of the new phosphonate reagents diethyl ethylformyl-2-phosphonate dimethylhydrazone (**2**) and diethyl 1-propylformyl-2-phosphonate dimethylhydrazone (**3**), compound **1** was prepared on a 10-g scale in just five steps (two condensation/deprotection cycles, plus a final Wittig olefination) from commercially available (2*E*)-2-methyl-2-butenal (**Scheme 1**), while the previous method (*14*) required seven steps. The Wittig olefination was further optimized during this study, by taking advantage of the observation that lithium cation (from *n*-butyllithium base) and increased concentration of the reactants can both lead to increased proportions of *E*-alkene (*15*). The overall yield and final purity of compound **1** were better than previously obtained (*14*). Further applications of the aldehyde dimethylhydrazone phosphonates are discussed.

MATERIALS AND METHODS

Chemicals and General Methods. Dry tetrahydrofuran (THF) was prepared by distillation from sodium benzophenone ketyl. Diethyl ethylphosphonate and diethyl 1-propylphosphonate were purchased from Alfa Aesar (Ward Hill, MA), but these compounds were also prepared in the laboratory (see below). Other organic reagents were obtained from Aldrich and were used without further purification. Nonaqueous reactions were performed under an atmosphere of dry argon in oven-dried glassware. Removal of solvent, during workups, was accomplished by rotary evaporation at water aspirator vacuum.

Analysis of Reaction Products. Progress of synthetic reactions was monitored by gas chromatography (GC) and GC mass spectrometry (GC-MS). The unwanted *Z*-isomer products were recognized by their shorter GC retention times but nearly identical mass spectra, compared to the *all-E*-isomers (*14*). Reported yields included only the *all-E* isomers. All structures and double-bond configurations were additionally verified by NMR.

The Hewlett-Packard (HP) 5890 Series II gas chromatograph was equipped with flame ionization detector and split/splitless inlet and was interfaced to an HP ChemStation data system. The column was a DB-5 capillary (30 m × 0.25 mm, 0.25-μm film thickness, J&W Scientific, Folsom, CA). Carrier gas was He. The oven temperature was programmed from 50 to 280 °C at 10 °C/min, and the detector temperature was 280 °C. The inlet temperature was 120 °C, and 1.0 μL sample injections were made in splitless mode. Considerable degradation of unsaturated aldehyde dimethylhydrazones was observed during GC runs with higher inlet temperatures, especially for compound **6**.

Electron impact mass spectra (70 eV) were obtained with an HP 5973 MSD instrument, interfaced to an HP 6890 GC, equipped with a splitless inlet. Several columns were used, but all gave comparable results to that used for GC. The oven temperature was programmed from 50 to 250 °C at 10 °C/min; the inlet temperature was 120 °C and the transfer line temperature was 250 °C.

^{1}H NMR, ^{13}C NMR, and 2D NMR spectra were collected on a Bruker (Bellerica, MA) Avance 500 spectrometer using a 5 mm inverse broadband probe. Samples were dissolved in $CDCl_3$ or C_6D_6 (compound **1**), and all spectra [^{1}H and correlation spectroscopy (COSY) at 500 MHz, ^{13}C and distortionless enhancement by polarization transfer (DEPT) at 125 MHz] were acquired at 300 K. Configurations of trisubstituted double bonds were assigned as *E* or *Z*, on the basis of one-and two-dimensional pulsed field gradient nuclear Overhauser enhancement spectroscopic (1D and 2D PFG-NOESY) experiments. Chemical shifts are reported as parts per million from tetramethylsilane. Coupling constants (*J*) are in hertz. Assignments for new compounds were made with the help of ^{1}H- and ^{13}C-Predictive software (*16*) and by analogy to known compounds.

Synthetic Details: *Diethyl Ethylphosphonate*. This compound was prepared in 98% yield by refluxing a mixture of triethyl phosphite and ethyl iodide for 3 h as described previously (*17*).

Diethyl 1-Propylphosphonate. A 250 mL round-bottomed flask containing 33.2 g (34.3 mL, 0.2 mol) of triethyl phosphite and 61.5 g (45.4 mL, 0.5 mol) of 1-bromopropane was fitted with a Vigreux column, thermometer, Dean−Stark trap, and an efficient water-cooled reflux condenser. The solution was magnetically stirred at reflux temperature, but only enough heat was applied to distill off the byproduct bromoethane as it was formed (bp 37−40 °C, compared to

bp 71 °C for 1-bromopropane). The reaction was monitored by GC and by measuring the volume of bromoethane in the Dean−Stark trap. The reaction was complete when the triethyl phosphite was consumed, which took 3−4 days. Kugelrohr distillation (32 °C oven temperature, 0.05 Torr) from two batches afforded 69.3 g (96% isolated yield, 95% purity). The main product was identical to commercially available diethyl 1-propylphosphonate in GC retention time and mass spectrum. The distilled product also contained 2% diethyl ethylphosphonate, resulting from reaction with byproduct bromoethane.

Diethyl Ethylformyl-2-phosphonate Dimethylhydrazone (**2**). A solution of *n*-butyllithium (2.5 M, 85 mL, 0.213 mol, slight excess) was added to dry THF (250 mL) and the mixture was cooled in an argon atmosphere to dry ice−ethanol bath temperature (approximately −78 °C). Diethyl ethylphosphonate (33.2 g, 32.4 mL, 0.20 mol) was added dropwise and the mixture was stirred for an additional hour before dry dimethylformamide (DMF, distilled from CaH_2, 20 mL, 0.26 mol) was added. After the solution warmed to 20 °C, ice-cold 3 M aqueous HCl (300 mL) was added and the mixture was stirred for 5 min. A fine white precipitate formed initially, and then the solution cleared and separated into two phases (liberation of the free phosphonate aldehyde). The phases were separated, and the organic phase was washed with 30 mL of alkaline brine solution (0.5% $NaHCO_3$ in saturated aqueous NaCl), dried over anhydrous $MgSO_4$, and filtered. The acidic aqueous phase was repeatedly extracted with CH_2Cl_2 (5 × 150 mL), and the combined CH_2Cl_2 extracts were washed with 30 mL of alkaline brine solution. The alkaline brine washes were combined and extracted again with CH_2Cl_2 (4 × 15 mL). All CH_2Cl_2 extracts were combined, dried over anhydrous $MgSO_4$, and filtered. Solvent was removed from the dried organic phase and all dried CH_2Cl_2 extracts to afford 44 g of crude diethyl ethylformyl-2-phosphonate, which still contained some DMF. Without further purification, the crude product was converted to the dimethylhydrazone (DMH) derivative by adding it to a mixture of CH_2Cl_2 (600 mL) containing anhydrous $MgSO_4$ (48 g, 0.4 mol); then *N*,*N*-dimethylhydrazine (15.6 g, 20 mL, 0.26 mol) was added in one portion. The mixture was stirred (48 h) until analysis by GC showed complete protection of the aldehyde as the DMH derivative. Filtration, removal of solvent, and Kugelrohr distillation (oven temperature 50 °C, 0.04 Torr) afforded 47.6 g of compound **2** (purity 98%, yield corrected for purity 97%). Isolated yields >95% were routinely obtained. MS (EI) *m*/*z* (%) 236 (M^+, 34), 194 (8), 166 (82), 136 (42), 122 (10), 111 (12), 99 (100), 53 (12), 81 (12), 72 (11), 56 (12), 44 (36). EI-HRMS calcd for $C_9H_{21}N_2O_3P$ 236.1290 (obsd 236.1293). ^{1}H NMR δ 1.19 and 1.20 (overlapping t, 6H, J = 7.0, CH_3−CH$_2$−O), 1.26 (d, 3H, J_{2-3} = 7.3 Hz, H-3), 2.76 (dq, 1H, J_{1-2} = 4.1 Hz and J_{2-3} = 7.3 Hz, H-2), 2.66 (s, 6H, N−CH_3), 3.99 and 4.00 (overlapping q, 4H, J = 7.0 Hz, CH$_3$−CH_2−O), 6.38 (br d, 1H, J_{1-2} = 4.1 Hz, H-1). ^{13}C NMR δ 12.7 (C-3), 16.4 (*C*H$_3$−CH$_2$−O), 36.0 and 37.1 (C-2, isomers), 43.1 (N−CH$_3$), 62.0 (CH$_3$−*C*H$_2$−O), 132.6 (C-1).

Diethyl 1-Propylformyl-2-phosphonate Dimethylhydrazone (**3**). A preparation similar to that of compound **2** but with diethyl 1-propylphosphonate (36.2 g, 36 mL, 0.20 mol) afforded 48 g of compound **3** (Kugelrohr oven temperature 68 °C, 0.05 Torr, purity 95%, yield corrected for purity 91%). MS (EI) *m*/*z* (%) 250 (M^+, 39), 235 (18), 208 (6), 206 (7), 180 (57), 165 (28), 150 (36), 53 (12), 113 (100), 83 (10), 81 (10), 70 (17), 44 (16). EI-HRMS calcd for $C_{10}H_{23}N_2O_3P$ 250.1446 (obsd 250.1449) ^{1}H NMR δ0.86 (t, 3H, J = 7.4 Hz, H-4), 1.18 and 1.19 (overlapping t, 3H, J = 7.3 Hz, CH_3−CH$_2$−O), 1.62 and 1.80 (m, 2H, H-3), 2.58 (m, 1H, H-2), 2.67 (s, 6H, N−CH$_3$), 3.97 and 3.98 (overlapping q, 4H, J = 7.3 Hz, CH$_3$−CH_2−O), 6.26 (br d, 1H, J = 3.8 Hz, H-1). ^{13}C NMR δ 12.3 (C-4), 16.4 (*C*H$_3$−CH$_2$−O), 20.8 (C-3), 43.2 (N−CH$_3$), 44.4 (C-2), 61.9 (CH$_3$−*C*H$_2$−O), 131.9 (C-1).

(2E,4E)-2,4-Dimethyl-2,4-hexadienal Dimethylhydrazone (**4**). A commercial 2.0 M solution of lithium diisopropylamide (LDA, 102 mL, 0.204 mol, slight excess) was added dropwise (reaction exothermic) to a 1 L round-bottomed flask containing dry THF (450 mL), compound **2** (47.2 g, 0.20 mol), and a few milligrams of ethyltriphenylphosphonium bromide, as an indicator, and the mixture was stirred in an argon atmosphere at room temperature (rt) for 1.5 h to ensure complete formation of the phosphonate ylide. A persistent red color developed in the solution when sufficient base was added to convert the phosphonate to its anion. Then (2*E*)-2-methyl-2-butenal (21.0 g, 0.25 mol) was added dropwise; final color was yellow-orange. The mixture was stirred at rt for 20 h. Consumption of the phosphonate **2** was monitored by GC. Water (50 mL) was added to quench the reaction (excess water should be avoided because it leads to problematic emulsions during subsequent extraction steps). The solvent was removed by rotary evaporation to give an oily residue, which was extracted with ethyl acetate (12 × 100 mL, but about 90% of the product was recovered with just five extractions). The combined extracts were dried over anhydrous Na_2SO_4 and filtered, and removal of solvent left a yellow oil. Kugelrohr distillation (oven temperature 38 °C, 0.05 Torr) afforded 27.9 g of compound **4** (91% purity by GC, yield corrected for purity 80%). By GC and GC-MS, the 2*E*/2*Z* isomer ratio was 46:1. MS (EI) *m*/*z* (%) 166 (M^+, 16), 151 (80), 137 (17), 121 (100), 106 (62), 79 (47), 77 (29), 53 (12), 44 (16), 39 (18). EI-HRMS calcd for $C_{10}H_{18}N_2$ 166.1470 (obsd 166.1475). ^{1}H NMR δ 1.74 (d, 3H, J_{5-6} = 7.2 Hz, H-6, see **Figure 1**), 1.86 (s, 3H, H-7), 2.03 (s, 3H, H-8), 2.86 (s, 6H, N−CH$_3$), 5.57, (q, 1H, J_{5-6} = 7.2 Hz, H-5), 6.02 (s, 1H, H-3), 7.14 (s, 1H, H-1). ^{13}C NMR δ 13.2 (C-8), 13.9 (C-6), 16.6 (C-7), 43.2 (N−CH$_3$), 126.4 (C-5), 132.7 (C-2), 133.8 (C-4), 136.3 (C-3), 141.8 (C-1).

(2E,4E)-2,4-Dimethyl-2,4-hexadienal (**5**). Deprotection was initiated by stirring compound **4** (12 g, containing 10.9 g of **4**, 0.066 mol) with 1 M HCl (750 mL) at room temperature for 5 min (compound **4** dissolves as the hydrochloride salt forms) and then petroleum ether (bp 35−60 °C, 750 mL) was added and stirring continued. After 3 h, the phases were separated and the aqueous phase was returned to the reaction vessel. Petroleum ether (750 mL) was added and the mixture was stirred at rt for an additional 1 h before the phases were separated. The combined petroleum ether phases were washed with alkaline brine solution (20 mL), and the brine phase was back-extracted once with petroleum ether (20 mL). The combined organic phases were dried, and removal of solvent afforded 8.36 g of the free aldehyde **5**. Over two batches, purity by GC was 92−96%, and yield corrected for purity was 94−98%. The 2*E*:2*Z* isomer ratio was 27:1. The MS and NMR spectral data were consistent with the reference spectral data from previous work (*14*).

(2E,4E,6E)-2-Ethyl-4,6-dimethyl-2,4,6-octatrienal Dimethylhydrazone (**6**). Compound **6** was prepared in a way similar to compound **4**. The phosphonate anion was prepared from **3** (38 g, 0.152 mol) in THF (400 mL) by treatment with LDA (2.0 M, 77 mL, 0.154 mol, slight excess); aldehyde **5** (18.6 g, containing 17.5 g of aldehyde **5**, 0.141 mol) was subsequently added and the reaction was completed as before. Kugelrohr distillation (oven temperature 56 °C, 0.06 Torr) afforded 32.0 g of compound **6**. By GC, minimum purity was 86%; actual purity may have been higher because some heat-related degradation was evident in the GC trace. Yield, corrected for purity, was ≥84%. The 2*E*:2*Z* isomer ratio was estimated to be 30:1 by NMR. MS (EI) *m*/*z* (%) 220 (M^+, 18), 205 (7), 191 (17), 175 (20), 165 (100), 160 (31), 146 (19), 122 (15), 107 (10), 105 (11), 91 (13), 59 (10), 44 (8). EI-HRMS calcd for $C_{14}H_{24}N_2$ 220.1939 (obsd 220.1939). ^{1}H NMR δ 1.47 (t, 3H, J_{11-12} = 7.4 Hz, H-12, see **Figure 1**), 1.71 (d, 3H, J_{7-8} = 6.9 Hz, H-8), 1.82 (s, 3H, H-9), 2.14 (s, 3H, H-10), 2.69 (s, 6H, N−CH$_3$), 3.01 (q, 2H, J_{11-12} = 7.4 Hz, H-11), 5.61 (q, 1H, J_{7-8} = 6.9 Hz, H-7), 6.15 (s, 1H, H-3), 6.24 (s, 1H, H-5), 7.00 (s, 1H, H-1). ^{13}C NMR δ 13.6 (C-9), 14.9 (C-12), 16.7 (C-8), 18.6 (C-10), 20.6 (C-11), 42.5 (N−CH$_3$), 125.0 (C-7), 132.5 (C-4), 133.7 (C-6), 134.7 (C-5), 135.7 (C-3), 138.1 (C-1), 140.6 (C-2).

(2E,4E,6E)-2-Ethyl-4,6-dimethyl-2,4,6-octatrienal (**7**). Deprotection procedure was similar to that used for compound **5**. A solution containing compound **6** (9.12 g, containing about 7.84 g of compound **6**, 35.6 mmol) and 1 M HCl (420 mL), to which petroleum ether (bp 35−60 °C, 420 mL) was added after 5 min, was stirred at room temperature for 13 h. After 13 h, the phases were separated and the aqueous phase was returned to the reaction vessel. Petroleum ether (400 mL) was added and the mixture was stirred at rt for an additional 4 h before the phases were separated. Completion of the reaction as for compound **5** resulted in 5.65 g of the free aldehyde **7** (purity by GC showed 84%, yield corrected for purity 75%). The 2*E*:2*Z* isomer ratio was 23:1. Two batches gave essentially identical results. The MS and

NMR spectral data were consistent with the reference spectral data from previous work (*14*).

(2E,4E,6E,8E)-3,5-Dimethyl-7-ethyl-2,4,6,8-undecatetraene (**1**). A slurry of propyl(triphenyl)phosphonium bromide (25.3 g, 65 mmol) was prepared in THF (50 mL) and chilled, in an argon atmosphere, over an ice−water bath. A solution of *n*-butyllithium (2.5 M in hexane) was added until the orange color persisted and then an additional 25 mL (62.5 mmol) was added slowly, with the temperature kept under 10 °C. After the solution was stirred for 1 h, crude (2*E*,4*E*,6*E*)-2-ethyl-4,6-dimethyl-2,4,6-octatrienal (**7**) (9.09 g, containing 41 mmol of the 2*E*,4*E*,6*E* isomer) was added dropwise, with the temperature kept below 10 °C. The mixture was allowed to warm to rt and was stirred for an additional 3 h. Methanol (100 mL) was then added; the red solution became turbid and then cleared and turned a light yellow color. Water (10 mL) was added and the solvent was removed by rotary evaporation to afford a viscous oil, which was extracted with hexane (3 × 100 mL). Removal of solvent resulted in a pale yellow oil (9.77 g). Analysis of two batches by GC showed the purity of compound **1** to be 65−68%, and the yield of compound **1** from *all-E*-**7**, corrected for purity, was 76−78%. The 8*E*:8*Z* isomer ratio for compound **1** was 7.5. The product contained about 9% 8*Z*-isomer and about 6% all other isomers of compound **1** by GC/MS analysis. A portion (2.7 g) of the material (produced without chromatography and distillation) was chromatographed as described in the earlier synthetic reference (*14*) and then Kugelrohr-distilled to determine if any improvement was observed following either purification step, as observed by GC/MS analysis. The MS and NMR spectral data were consistent with the reference spectral data from previous work (*13, 14*).

The effect of concentration on the *E*/*Z* isomer ratio for the final Wittig reaction was studied on a small scale. Propyl(triphenyl)-phosphonium bromide (500 mg, 1.3 mmol), 1.25 mmol of nBuLi (0.5 mL), aldehyde **7** (178 mg of the material described above with 82% 2*E*,4*E*,6*E* isomer, 1 mmol), and various amounts of THF were used. Reactions were conducted as above for the preparation of compound **1**. An additional experiment, to study the effect of increasing the ylide to aldehyde ratio, was conducted with 2.9 mL of THF in which 1.1× phosphonium salt and 1.05× nBuLi was compared with 1.3× phosphonium salt and 1.25× nBuLi.

RESULTS AND DISCUSSION

The synthetic pathway to pheromone **1** (**Scheme 1**) was shortened from seven steps to five steps, and the previous reduction and oxidation steps are no longer required. The key advance was the use of the new dimethylhydrazone phosphonate reagents **2** and **3**, which can be made from either laboratory-prepared or commercially available diethyl ethylphosphonate and diethyl 1-propylphosphonate. The new phosphonate reagents were used to accomplish the robust and direct two-carbon homologation of aldehydes to methyl- and ethyl-branched α,β-unsaturated aldehydes, protected as dimethylhydrazones, and a facile deprotection step then liberated the desired aldehyde products. The final Wittig reaction in the synthesis of **1** was optimized by using a relatively concentrated solution of the phosphonium ylide in THF, which maximized the ratio of 8*E* to 8*Z* products, and an improved workup was developed for removing byproduct triphenylphosphine oxide.

The new phosphonate reagents were synthesized from diethyl alkylphosphonate starting materials. Diethyl alkylphosphonate starting materials were formylated, and then the aldehyde functional group was protected as the dimethylhydrazone derivative to prepare the new phosphonate reagents. Aldehyde phosphonates, such as ethylformyl-2-phosphonate and diethyl 1-propylformyl-2-phosphonate, were readily prepared by the method of Aboujaoude and Collignon (*5*), and these were converted essentially quantitatively to the dimethylhydrazone derivatives **2** and **3** (*10*). The new method requires the phosphonate reagents to be synthesized, whereas those for the original method were available commercially. Nevertheless,

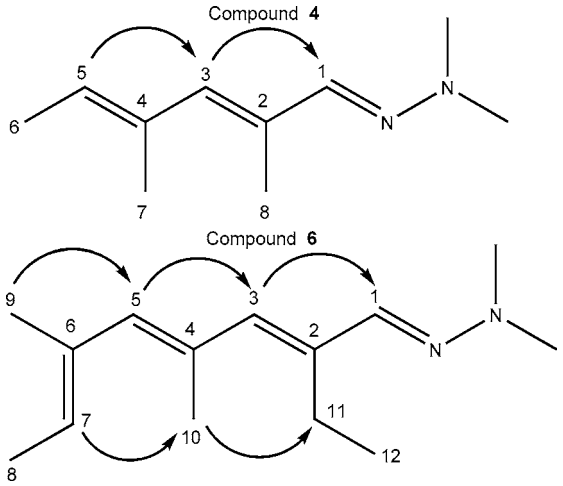


Figure 1. Observed nuclear Overhauser enhancements (>0.5%) used to assign configurations of trisubstituted double bonds of compounds **4** and **6**.

large batches of the new reagents can be prepared and stored, and these stocks could subsequently serve for syntheses of a variety of final products. Alternative names for the aldehyde phosphonates and aldehyde phosphonate dimethylhydrazones **2** and **3** are given in the reference section (*18*). We chose to use the simpler, and more intuitive, names in this paper.

The new phosphonate reagents were readily converted to their anions with the LDA base and reacted smoothly with aldehydes to give alkyl-branched, unsaturated aldehyde dimethylhydrazones with chains having two additional carbons (**4** and **6**, **Scheme 1**). Spectral data for new compounds **4** and **6** are reported. The nuclear Overhauser experiment (NOE) results for compounds **4** and **6** are summarized in **Figure 1**. These observations support the assignment of *E*-configuration at all the trisubstituted double bonds for compounds **4** and **6**.

Deprotection of aldehyde dimethylhydrazone compounds **4** and **6** was accomplished by use of a biphasic mixture of 1 M HCl and petroleum ether (*11*). In the deprotection reaction, the dimethylhydrazone is initially converted to a water-soluble hydrochloride salt, and the free aldehyde then forms under acidic conditions. Successful deprotection requires immediate migration of the liberated, but rather labile, aldehyde from the aqueous phase to the neutral petroleum ether phase. This procedure gave a favorable (27:1) ratio of 2*E* to 2*Z* products. In the absence of petroleum ether, dimethylhydrazone **4** gave a complex mixture of reaction products. Deprotection of compound **4** was also accomplished with 50% aqueous glyoxylic acid (*10*), but the 2*E*:2*Z* ratio fell to only 7.7:1, and deprotection of **6** with 50% aqueous glyoxylic acid resulted in a yield of only 18%, along with a tarlike material.

In our experience, the final Wittig reaction has given variable results with respect to the *E*:*Z* isomer ratio, and efforts were made to optimize the yield of the *E* isomers. It is known that lithium cation (from *n*-butyllithium base) and increased concentration of the reactants can both lead to increased proportions of *E*-alkene (*15*). Therefore, we studied the effect of reactant concentration on the product **1** isomer ratio (**Table 1**). The 8*E*/8*Z* isomer ratio increased as the volume of solvent decreased. The best results were obtained by using a relatively concentrated solution of reactants (i.e., 1 M aldehyde and 1.25 M phosphonium ylide). In a separate experiment, we found that increasing the amount of excess phosphonium ylide was beneficial. The 8*E*/8*Z* isomer ratio increased from 3.5:1 to 5.4:1 when the ylide to aldehyde ratio was increased from 1.05:1 to 1.25:1.

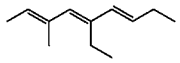
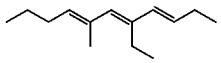
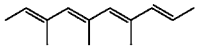
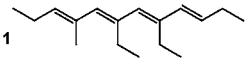
	Compound	Starting material	Condensation cycles with	Wittig reagent: Alkyl $Ph_3P^+Br^-$
8		(2*E*)-2-methyl -2-butenal	3	Propyl
9		butanal	2, 3	Propyl
10		(2*E*)-2-methyl -2-butenal	2, 2	Ethyl
11		(2*E*)-2-methyl -2-pentenal	3, 3	Propyl

Figure 2. Examples of *Carpophilus* beetle pheromones (*12*) that could be prepared via the new synthetic pathway.

Table 1. Effect of Reactant Concentration on Product **1** Isomer Ratio[a]

volume of THF (mL)	8*E*:8*Z* ratio
20	1.1
5	2.6
2.9	5.4
1	9.2

[a] The reactions were run on a 1 mmol scale, with 1.3 mmol of propyl(triphenyl)phosphonium bromide (500 mg), varying amounts of THF, 1.25 mmol of *n*-BuLi (0.5 mL), and 1 mmol of (2*E*,4*E*,6*E*)-2-ethyl-4,6-dimethyl-2,4,6-octatrienal (**7**) (178 mg of the material described in text, of which 82% was the 2*E*,4*E*,6*E* isomer). Reactions were conducted as explained for the preparation of compound **1**.

The workup of the preparative-scale Wittig reaction was improved. The reaction was quenched by adding methanol and a small amount of water, which converts any alkoxide base into hydroxide base. After the THF is removed by rotary evaporation, the triphenylphosphine oxide byproduct remains in an oily state, dissolved in the remaining methanol−water mixture. Extraction of the resulting oil with hexane and subsequent drying, filtration, and removal of solvent afforded an oil containing product **1** with almost none of the byproduct triphenylphosphine oxide. The purity of the product was as high as the product obtained after silica gel column chromatography, followed by Kugelrohr distillation (*14*). No purity improvement was observed (GC/MS analysis) following the additional purification steps because the major impurities (e.g., triphenylphosphine oxide) had already been removed. This new workup also improves the commercial viability of pheromone production.

Although the diethyl alkylphosphonate starting materials are commercially available, it is shown here that they can be readily prepared in the laboratory from less expensive starting materials (triethyl phosphite and alkyl halides). The preparation of diethyl 1-propylphosphonate requires removal of byproduct bromoethane, as it is formed, because the bromoethane will attack triethyl phosphite to form diethyl ethylphosphonate (*17*). However, attempts to prepare diethyl 1-propylphosphonate from ethyl phosphate and *n*-propyllithium (*19*), prepared in situ from *n*-propyl bromide and lithium metal, were not successful in our hands.

All reactions in the new synthetic pathway were conducted on a scale large enough (greater than 10 g) to ensure that the steps could be scaled up for commercial pheromone production. Yields of products for the five steps in the synthetic pathway were **4** (80%), **5** (96%), **6** (84%), **7** (75%), and **1** (77%), giving an overall yield of 37% from (2*E*)-2-methyl-2-butenal. This is a substantial improvement over the 20% overall yield for the previous seven-step pathway (*14*). Furthermore, the new method eliminates the use and disposal of some metal-containing reagents (reducing agents such as lithium aluminum hydride and oxidants such as manganese dioxide).

Other sap-beetle pheromones, such as compounds **8**−**11** in **Figure 2**, could be prepared by this new chemistry as well, with the appropriate choice of starting materials, dimethylhydrazone phosphonates, number of condensation cycles, and final Wittig reagents. Overall, the starting materials are sufficiently inexpensive and the reactions and intermediates are sufficiently robust so that the pathway can be commercially viable. Beyond nitidulid pheromones, this more concise chemistry could be applied to the practical synthesis of a variety of natural products, pharmaceuticals, and other compounds. An unbranched phosphonate, diethyl methylformyl-2-phosphonate dimethylhydrazone, will be the subject of a future paper.

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