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Improved synthesis of (9*Z*)-9,13-tetradecadien-11-ynal, the sex pheromone of the avocado seed moth, *Stenoma catenifer*

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ABSTRACT

The terminal dienyne of (9*Z*)-9,13-tetradecadien-11-ynal, the sex pheromone of the avocado seed moth, *Stenoma catenifer*, was constructed by coupling a vinyl iodide precursor with commercially available 1-buten-3-yne with Pd catalysis, resulting in a short and efficient synthesis of the pheromone.

The avocado seed moth, *Stenoma catenifer*, is a major pest of commercial avocado production in South and Central America, with damage in some areas being so severe that the insect limits or even prevents commercial cultivation of avocadoes.[1] However, the seed moth has not yet become established in avocado production areas of the United States, although United States Department of Agriculture risk assessments have identified *S. catenifer* as one of the most serious threats to the US avocado industry.[2]

As part of an ongoing project to provide growers, exporters, and regulatory agencies with a method for detection of *S. catenifer*, we recently identified (9*Z*)-9,13-tetradecadien-11-ynal **1** as the sex attractant pheromone of the seed moth.[3] Field trials have now verified the biological activity of the pheromone, and protocols for its use have been worked out.[4] However, commercialization of the pheromone has been slowed by the relatively inefficient synthesis used for its production, particularly the multistep construction of the terminal dienyne unit. Because we did not initially know the relative positions or stereochemistry of the alkene and alkyne bonds in the pheromone, our original synthesis[3] was designed to be flexible so that each of the two alkenes and the alkyne in the conjugated system could be installed in any one of the three possible positions. This requirement for flexibility resulted in the synthesis being longer than might be required for a single specific target. Improvements in the efficiency of several steps increased the overall yield, but still required a three-step sequence to assemble the terminal dienyne (Sonogashira coupling of an alkenyl iodide with propargyl alcohol, oxidation of the resulting propargyl alcohol to the aldehyde, and installation of the terminal double bond with a Wittig reaction).[3] It occurred to us that it might be possible to install the terminal enyne in a single step via a Sonogashira coupling between the vinyl iodide **4** and commercially available 1-buten-3-yne (vinyl acetylene). A survey of the literature revealed only a single report of this type of coupling. Specifically, De Meijere and co-workers showed that various 1,5-dien-3-ynes could be prepared by Sonogashira coupling of an alkenyl halide with a substituted enyne.[5] However, when 1-buten-3-yne was used, the yield was low and styrene was identified as the major product from a palladium-catalyzed formal [4+2] cycloaddition between two vinyl acetylene molecules.[5] In addition to this undesired side reaction, a further concern that became apparent for our particular application was that **4** and **5** have almost the same TLC R_f value and GC retention time. Therefore, if the reaction did not go to completion, separation of the product from unreacted starting material would be difficult, particularly on the larger scales required for commercially useful s\yntheses. After some experimentation with various ratios of the vinyl iodide **4** and vinyl acetylene, we found that the desired Sonogashira coupling proceeded cleanly to give the desired dienyne product, with complete consumption of the starting material, using 2.5 or more equivalents[6] of commercial 1-buten-3-yne (41.1 wt % in xylene; GFS Chemicals), producing dienynal **1** in five steps from the readily available starting material **2** (Fig. 1).

Thus, deprotonation of a THF solution of THP-protected 9-decyn-1-ol **2**[7] with BuLi at −78 °C, followed by the addition of a solution of iodine in THF gave iodoalkyne **3**.[4,8] Stereospecific reduction with dicyclohexylborane in THF followed by protonolysis gave *Z*-iodoalkene **4**.[4,9] Sonogashira coupling of the iodoalkene with

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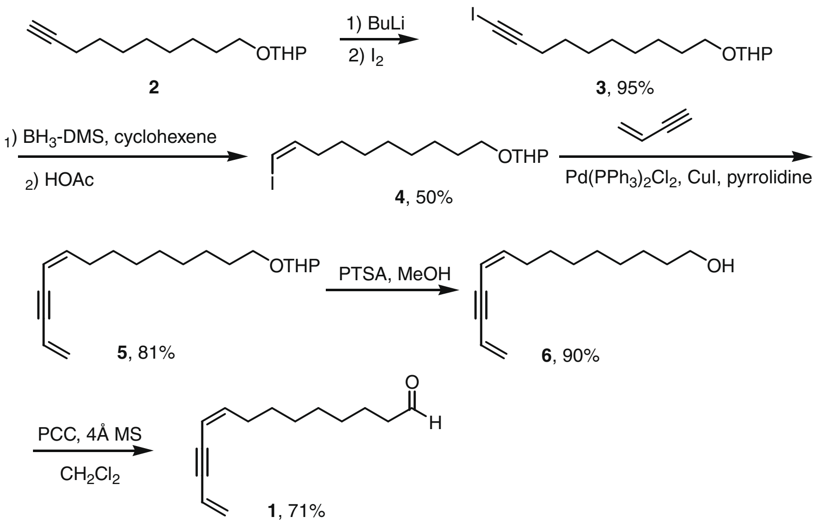

Figure 1. Synthesis of (9*Z*)-9,13-tetradecadien-11-ynal.

2.5 equiv of vinyl acetylene in pyrrolidine at 0 °C resulted in complete consumption of the starting material, yielding the pure dienyne **5** in 81% isolated yield.[10] The synthesis was completed by straightforward removal of the THP-protecting group (PTSA in MeOH; 90% purified yield), and pyridinium chlorochromate oxidation of the resulting alcohol **6** to yield the target aldehyde **1** (71%).[11] This short and efficient synthesis is now under commercial development to produce the pheromone for use throughout Central America, South America, and California.

Acknowledgments

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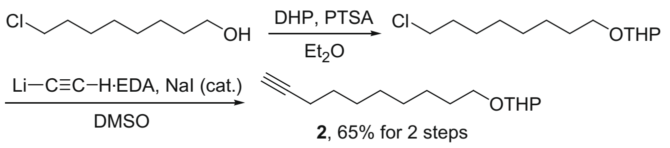
6. With 2 equiv of 1-buten-3-yne (41.1 wt % in xylene), the product was obtained in moderate yield with some unreacted starting material.
7. 2-(9-Decynyloxy)-tetrahydropyran **2** was prepared from 8-chloro-octan-1-ol in two steps.



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10. *(9Z)-Tetradeca-9,13-dien-11-yn-1-ol* (**6**): A dry two-necked flask under Ar was loaded with bis(triphenyl-phosphine)palladium(II) dichloride (0.069 g, 0.098 mmol), CuI (0.037 g, 0.19 mmol), and pyrrolidine (5 mL), and the mixture was cooled to 0 °C. Iodide **4** (1.43 g, 3.91 mmol) in pyrrolidine (3 mL) was added dropwise, followed by dropwise addition of 1-buten-3-yne (1.24 g of a 41.1% xylene solution, 9.79 mmol; GFS Chemicals, Powell, OH). The reaction mixture was stirred for 3 h while gradually warming to room temperature, then poured into ice-cold 1 M KH_2PO_4 solution and extracted with hexanes. The combined organic layer was washed with water and brine, dried, and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/Et_2O = 95/5) to give 0.92 g (81%) of 2-(tetradeca-9,13-dien-11-yn-1-yloxy)tetrahydro-2*H*-pyran **5** as a light yellow oil, which was dissolved in MeOH (8 mL) and stirred with PTSA (0.030 g, 0.16 mmol) for 2.5 h. The mixture was diluted with hexanes, washed with saturated aqueous $NaHCO_3$ and brine, then dried and concentrated. The crude product was purified by vacuum flash chromatography on silica gel (hexanes/EtOAc = 9/1 to 5/1) to give 0.59 g (90%) of **6** as a colorless oil. The ^1H NMR spectrum was consistent with that described previously.[3]
11. *Spectral data for (9Z)-9,13-tetradecadien-11-ynal* (**1**): ^1H NMR: δ 9.75 (t, J = 2.0 Hz, 1H), 5.92 (m, 2H), 5.60 (dd, J = 17.6, 2.4 Hz, 1H), 5.56 (dd, J = 11.2, 1.6 Hz, 1H), 5.45 (dd, J = 11.2, 1.6 Hz, 1H), 2.41 (td, J = 7.4, 2.0 Hz, 2H), 2.30 (qd, J = 7.3, 1.6 Hz, 2H), 1.62 (m, 2H), 1.44–1.28 (m, 8H). ^{13}C NMR: δ 203.0 (CH), 144.4 (CH), 126.2 (CH_2), 117.6 (CH), 109.1 (CH), 92.4 (C), 87.2 (C), 44.1 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 22.2 (CH_2). IR (neat): 3018, 2928, 2856, 2719, 1724, 1599, 1464, 1414, 1392, 1164, 971, 917, 738, 674 cm^{-1}. HRMS (ESI/APCI) calcd for $C_{14}H_{21}O$ $[M+H]^+$: 205.1592, found 205.1589.