# Improved synthesis of (*Z,E*)-9,11,13-tetradecatrienal, the sex pheromone of the Carob Moth *Apomyelois* (=*Ectomyelois*) *ceratoniae* (Lepidoptera: Pyralidae)

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(*Z,E*)-9,11,13-Tetradecatrienal is a sex pheromone component emitted by virgin females of the Carob Moth *Apomyelois ceratoniae* Zeller (Lepidoptera: Pyralidae) which is an important pest of Iranian pomegranate fruits. Chemical control of this pest is not possible and biological methods with pheromones are used. The synthesis of the major component of the sex pheromone was achieved in fewer steps and with lower cost than previously. (*Z,E*)-9,11,13-Tetradecatrienal was synthesised by four steps with 59% overall yield. The coupling of a conjugated dienynol intermediate from *E*-1,2-dichloroethylene with vinyl magnesium bromide was achieved in good yield and followed by reduction of dienynol with activated zinc in THF-$H_2O$ and oxidation gave the aldehyde of the sex pheromone.

**Keywords:** synthesis, sex pheromone, stereoselective reduction

(*Z,E*)-9,11,13-Tetradecatrienal was isolated and synthesised by Millar (1990) as a component of the sex pheromone of the female Carob Moth, *Apomyelois ceratoniae*.[1] This insect is a worldwide pest of nuts and fruits including, in the United States, carobs, almonds, and dates. Moreover, in other parts of the world, this species is a primary pest of dates, almond and pistachio, and in Iran, an important pest of pomegranates.[2,3,4] Mining by larvae can damage the fruit introducing fungal saprophytes, rendering the fruit unacceptable for the fresh fruit market. Larvae remain protected for almost their entire development within the mines limiting the effectiveness of chemical control. There are many generations per year in different parts of Iran, and typically three to four generations can cause damage to fruit.[5,6] Insect pest management, monitoring and control programmes utilising sex pheromones as behaviour modifying chemicals have become necessary for several insect groups, particularly moths. Thus, a pheromone-based method for sampling *A. ceratoniae* populations by using traps to catch the adult male moths might provide a method for timing and so maximising the efficacy of control.

(8*E*,10*E*)-Tetradecadienal is a sex pheromone component of *Marmara gulosa* Guillén and Davis (Lepidoptera: Gracillariidae), which is a sporadic pest of citrus and a number of other crops. It was synthesised and used as a reliable and accurate tool for monitoring densities of *M. gulosa*.[7] The *Z*-isomer of the sex pheromone of the female Douglas Fir Cone Gall Midge, tridecadien-2-yl acetate with non-conjugated double bonds, was synthesised from a diyene by reduction over P-2 nickel in good yield. In Douglas Fir seed orchards, sticky traps baited with 2S-Z4-Z7 captured the male *Contarinia oregonensis* (Diptera: Cecidomyiidae).[8] Reduction of an alkyne stereoselectively to the *cis* or *trans* isomer is always a challenge in sex pheromone synthesis, and many reactions have been examined. In this regard, (*Z,Z*)-9,11-tetradecadienyl acetate, as a minor component of the sex pheromone gland of the Egyptian Cotton Leaf Worm, was stereoselectively reduced to the (*Z,Z*)-conjugated diene by Zn(Cu/Ag)/MeOH/$H_2$.[9]

Three pheromone components including (*Z,E*)-9,11,13-tetradecatrienal, (*Z,E*)-9,11-tetradecadienal and (*Z*)-9-tetradecenal of *A. ceratoniae* were extracted by solvent. The first component, which was mentioned above, is quite active in attracting males in biological assays and field tests by itself. The former major component has been synthesised in several steps.[10,11] Our synthesis of (*Z,E*)-9,11,13-tetradecatrienal improved the yield and removed two steps[1] which had limited its availability and were costly. We synthesised the major trienal aldehyde in a shorter route in which the conjugated double bonds (C9) were introduced with a high degree of stereochemical control (Fig. 1).

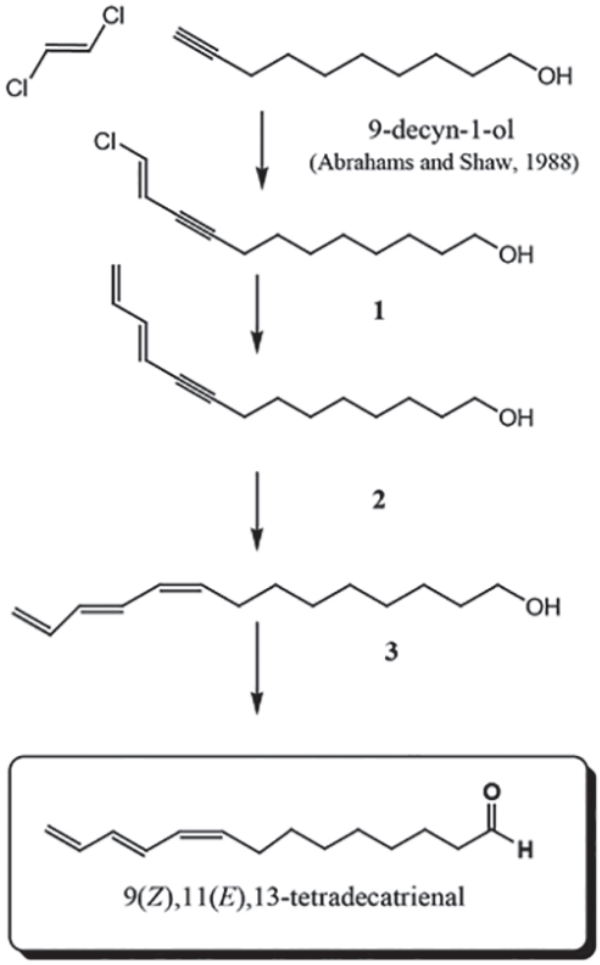

**Fig. 1** Synthesis of (*Z,E*)-9,11,13-tetradecatrienal.

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## Results and discussion

9-Decyn-1-ol was prepared from 3-decyn-l-ol in 85% yield *via* reaction with lithium amide to rearrange the alkyne bond to the terminal position.[12] The intermediate terminal alkyne was then coupled with *E*-l,2-dichloroethylene to afford the alcohol **1**, using a $(Ph_3P)_2PdCl_2$ catalyst, and THF as the solvent. A slurry of 9-decyn-1-ol (1 equiv.), *E*-l,2-dichloroethylene (2.5 equiv.), $(Ph_3P)_2PdCl_2$ (0.035 equiv.), CuI (0.13 equiv.) and diisopropylamine (2 equiv.) in THF, was stirred at 25 ºC for 24 h, to give the chloroalcohol **1** in 89% yield. Compound **1** was not protected as the THP ether and directly reacted with 2 equiv. vinylmagnesium bromides in toluene, with $(Ph_3P)_4Pd$ catalyst[11], yielding **2** in 84% isolated yield. In this study, it was found that the reduction of **2** proceeded at a satisfactory rate in THF: water (8:2) at room temperature, using zinc granules activated simply by stirring with dilute HCl. Alcohol **3** was obtained in good yield with no detectable isomer of the $C_{11}$ double bond or the newly formed $C_9$ double bond. It was stereochemically pure by NMR and GC/MS. The stereochemistry of the new olfin bond between $C_9$–H and $C_{10}$–H was established as the (*Z*)-isomer on the basis of the coupling constant *J* = 10.7 Hz ($^1$H NMR, δ: 5.48 and 6.09) which is lower than (*E*)-isomer coupling mentioned in references (*J* = 15 Hz).[13,14] This method, as originally reported, used zinc powder in refluxing aqueous 1-propanol, was further improved by activating the zinc dust with copper and silver salts.[15] These authors and others also reported that several other methods (Lindlar catalyst/$H_2$) for stereo- and regioselectively reducing the conjugated dienynes **2** were not satisfactory, giving mixtures of products. Alcohol **3** was obtained in good yield with no detectable isomerisation of either the $C_{11}$ double bond or the newly formed $C_9$ double bond. However, Millar (1990) reported that the product was contaminated by about 6% of an unidentified rearrangement product, which was removed by recrystallisaing the *p*-nitrobenzoate derivative of **3**. But, in our case, we could not separate these contaminants by crystallisation in toluene at –20 °C. Purity of compound **3** is very important for biological activity. In other words, the reduction of alkyne by $Pd/BaSO_4$ and $H_2$ resulted in alcohol **3** which was followed by oxidation. The trienal was ineffective in biological activity. The synthesis was completed by oxidation of the alcohol **3** to the target aldehyde. A pyridinium chlorochromate/molecular sieve mixture was used, as had been previously reported. The product was kept at –20 °C in a dark place until it was used.

## Experimental

(*Z,E*)-9,11,13-Tetradecatrienal was synthesised by a modified Millar (1990) method (Fig. 1).[1] Tetrahydrofuran (THF) was distilled from the sodium/benzophenone ketyl under $N_2$. Extracts were dried over anhydrous $Na_2SO_4$, and concentrated with a rotary evaporator under reduced pressure. Crude products were purified by flash or vacuum flash chromatography on silica gel (230–400 mesh). Reactions with air or water sensitive reagents were carried out in dried glassware under $N_2$ atmosphere. All samples were analysed by GC/MS on a fused capillary column HP5-MS (30 m length, 0.25 mm I.D., 0.25 mm film thickness, Agilent) in an Agilent. 6890 chromatograph equipped with the mass selective detector Agilent 5973 in the following conditions: the injector temperature was held at 250 °C; He as carrier gas at l mL min$^{-1}$; oven temperature programme, 5 min isotherm at 45 °C followed by linear temperature increase of 4º C min$^{-1}$ up to 300 °C held for 10 min. All chemicals and reagents were obtained from Merck and Sigma-Aldrich. $^1$H NMR spectra were measured using a Bruker 500 MHz spectrometer (Brucker, Rheinstetten, Germany). Chemical shifts were expressed as δ (ppm) with tetramethylsilane as internal standard. The infrared (IR) spectra were obtained on a Shimadzu IR prestige-21. The purity of all compounds was confirmed by thin-layer chromatography (TLC) using various mobile phases. The elemental analysis was performed with an Elementar Analysensystem GmbH Vario EL CHNS mode, which were within ±0.4% of theoretical values for C, H, and N.

### *(E)-1-Chloro-dodec-l-en-3-yn-12-ol* (**1**)

A dry 50 mL flask was loaded with bis(triphenylphosphine) palladium(II) chloride (300 mg, 0.45 mmol) and CuI (160 mg, 0.8 mmol) and flushed with argon. 9-Decyn-1-ol (1 g, 7.5 mmol) which was prepared by zipper reaction from 3-decyn-1-ol,[13] *trans*-1,2-dichloroethylene (0.13 mL, 1.7 mmol), and THF (3 mL) were added to the reaction flask. Diisopropylamine (0.18 mL, 1.3 mmol) was then added dropwise to the stirred mixture, and the initially pale yellow solution rapidly turned into brown and then black. The mixture was stirred at room temperature for 1 day. Hexane (20 mL) was then added, and the mixture was filtered. The filtrate was extracted by saturated aqueous $NH_4Cl$ (2 × 3 mL), dried and passed through a column of silica gel, and eluted with 20% EtOAc in hexane. The eluate was concentrated, yielding 1.2 g (5.6 mmol) (89% yield) of chloroalcohol (**1**). $^1$HNMR δ: 1.21–1.44 (m, 8H, H7, 8, 9, 10), 1.45–1.6 (m, 5H, H6, 11, OH), 2.28 (td, 2H, *J* = 6.8, 2.2 Hz, H5), 3.65 (t, 2H, *J* = 6.7 Hz, H12), 5.92 (dt, 1H, *J* = 13.5, 2.3 Hz, H2), 643 (d, 1H, *J* = 13.5 Hz, H1). MS *m/z:* 179 (M-Cl), 114, 105, 91, 79 (100), 67, 55. Anal. calcd for $C_{17}H_{27}ClO_2$: C, 68.32; H, 9.11; found: C, 68.12; H, 9.32%.

### *11(E),13-Tetradecadien-9-yn-1-ol* (**2**)

Tetrakis (triphenylphosphine) palladium (0.3 g, 0.26 mmol) and chloride **1** (1.3 g, 4.4 mmol) were added to toluene (10 mL) under $N_2$ at room temperature. The mixture was cooled in an ice-bath while vinyl magnesium bromide (9 mL of a 1 M solution in THF) was added dropwise over 5 min. The mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into hexane (30 mL), extracted thoroughly with 2 M $NH_4Cl$ and brine, dried, and concentrated under vacuum, to give the dienynol **2** as a yellow oil (0.72 g, 3.4 mmol) 79% yield. $^1$HNMR δ: 1.24–1.46 (m, 8H, H3, 4, 5, 6), 1.46–1.65 (m, 5H, H2, 7, OH), 2.33 (td, 2H, *J* = 6.9, 2.2 Hz, H8), 3.65 (t, 2H, *J* = 6.6 Hz, H1), 5.12 (d, 1H, *J* = 9.7 Hz, H14), 5.25 (br.d, 1H, *J* = 16.5 Hz, H14), 5.62 (dt, IH, *J* = 15.6, 2.0 Hz, H11), 6.35 (dt, 1H, *J* = 16.5, 10.0 Hz, H13), 6.51 (dd, 1H, *J* = 10.9, 15.4 Hz). IR cm$^{-1}$: 3333 (s, br.), 2932 (s). MS *m/z:* 206 ($M^+$), 105, 91 (100), 79, 65, 41. Anal. calcd for $C_{14}H_{22}O$: C, 80.50; H, 10.75; found: C, 80.77; H, 10.86%.

### *(Z,E)-9,11,13-Tetradecatrienol* (**3**)

Zinc dust (2.39 g, 46.50 mmol) was stirred three times with HCl (3%) (6 mL) for 2 min under argon. The acid was decanted and the zinc was rinsed twice with distilled water and added to a flask containing THF (8 mL) and $H_2O$ (2 mL), followed by a solution of the dienynol **2** (0.3 g, 1.45 mmol) in THF (1 mL). The mixture was stirred for 72 h at 25 °C under argon, then filtered, and washed with THF (10 mL). The filtrate was concentrated and residue was extracted with $Et_2O$:hexane (1:1), aq. sat. $NH_4Cl$, dried over $MgSO_4$, and concentrated, and purified by vacuum flash chromatography on silica gel (hexane/EtOAc, 95:5) giving the olefin **3** as a colourless oil (0.32 g, 1.45 mmol, quantitative yield). $^1$HNMR δ: 1.2–1.45 (m, 8H, H3, 4, 5, 6), 1.5–1.65 (m, 4H, H2, 7), 2.19 (br. quartet, 2H, *J* = 6.8 Hz, H8), 2.37 (s, lH, OH), 3.64 (t, 2H, *J* = 6.6 Hz, Hl), 5.08 (d, lH, *J* = 10.2 Hz, H14), 5.21 (d, lH, *J* = 15.6 Hz, H14’), 5.48 (dt, lH, *J* = 10.7, 7.7 Hz, H9), 6.02 (br. t, lH, *J* = 11.0 Hz, H10), 6.20 (dd, lH, *J* = 14.9, 10.7 Hz, H12), 6.41 (dt, lH, *J* = 16.8, 10.3 Hz, H13), 6.51 (dd, lH, *J* = 14.8, 11.3 Hz, H11). IR cm$^{-1}$: 3345 (s), 2940 (s), 1005 (s). MS *m/z:* 208 ($M^+$), 107, 91, 79 (100), 67. Anal. calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61; found: C, 80.87; H, 11.53%.

### *(Z,E)-9,11,13-Tetradecatrienal*

The trienol **3** was converted to corresponding aldehyde by pyridinium chlorochromate (PCC) oxidation.[14] $CH_2Cl_2$ (10 mL) and PCC (0.36 g, 1.68 mmol) and powdered molecular sieve were placed in a flask. Alcohol **3** (0.18 g, 0.84 mmol) in $CH_2Cl_2$ (2 mL) was added to this solution, and the mixture was stirred for 6 h. Hexane was then added, and the mixture was stirred for 10 min and then filtered. The filtrate was dried, concentrated, and then flash chromatographed ($SiO_2$), to give 9($Z$),11($E$),13-tetradecatrienal as a colourless oil (0.14 g, 0.7 mmol, 83%). $^1$H NMR (500 MHz, $CDCl_3$) δ: 1.24–1.31 (m, 8H, H4, 5, 6, 7), 1.55–1.62 (m, 2H, H3), 2.18 (brq, 2H, $J$ = 6.8 Hz, H8), 2.42 (td, 2H, $J$ = 7.0, 2.0 Hz, H2), 5.09 (d, 1H, $J$ = 10.0 Hz, H14), 5.22 (d, 1H, $J$ = 16.8 Hz, H14`), 5.47 (dt, 1H, $J$ = 10.8, 7.6 Hz, H9), 6.02 (brt, 1H, $J$ = 10.8 Hz, H10), 6.20 (dd, 1H, $J$ = 15.2, 10.8 Hz, H12), 6.41 (dt, 1H, $J$ = 16.8, 10.4 Hz, H13), 6.41 (dt, 1H, $J$ = 16.8, 10.4 Hz, H13), 6.50 (dd, 1H, $J$ = 15.2, 11.6 Hz, H11), 9.78 (t, 1H, $J$ = 2 Hz, aldehyde H). IR cm$^{-1}$: 3040 (w), 2940 (s), 2747 (m), 1730 (s), 1008 (s), 945 (m). MS $m/z$: 207, 206 ($M^+$), 178, 135, 121, 107, 94, 93, 91, 79 (100), 77, 67, 41. Anal. calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75; found: C, 81.66; H, 10.56%.

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