TOTAL STEREOSPECIFIC SYNTHESIS OF (3*E*,7*Z*)-TETRADECADIENYL ACETATE, THE MAJOR SEX PHEROMONE COMPONENT OF THE POTATO PEST *Symmetrischema tangolias*

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(3*E*,7*Z*)-Tetradecadienyl acetate, the major sex pheromone component of the potato pest *Symmetrischema tangolias* (Gyen), was stereoselectively synthesized from the commercially available 3-bromo-1-propanol via the stereospecific reduction of alkyne with lithium aluminum hydride (LAH) and the Wittig reaction.

Keywords: (3*E*,7*Z*)-tetradecadienyl acetate, pheromones, *Symmetrischema tangolias*, reduction, W ittig reaction, green metrics calculation.

Solanum tuberosum L. (potato) is cultivated all around the world because of its significance in human consumption and one of the cheapest staple food materials and richest sourcea of starch, dietary fibers, vitamins, and minerals. Thus, such a noteworthy crop is produced predominantly throughout the world, but this crop is severely damaged by various pests. To overcome such problems, researcher are making efforts towards controlling such pests by various measures such as use of chemical pesticides, biopesticides, and pheromones [1].

For environment friendly agriculture, two best practices are accessible, such as integrated crop management (ICM) and integrated iest management (IPM) [2]. Among them, in the ICM system the pheromones are the most frequently used and the most rapid technique for mating disruption, controlling pest, and mass trapping [3].

A literature review reveals that significant effort has been focused on the eco-friendly synthesis of sex pheromones by multistep reaction pathways, among which are protection [4], alkylation [5], reduction [6], acetylation [7], oxidation [8], and the Wittig reaction [9]; these are most widely used reactions towards the synthesis of various sex pheromones of the female moth.

The potato tuber moth *Symmetrischema tangolias* (Gyen) is recognized as a severe pest on potatoes in the field as well as in storehouses [10].

The use of insect pheromones by mass trapping and mating disruption techniques has shown promising results in controlling distressing insect pests [11].

There are very few reports on identification and synthesis of sex pheromone. In 1995 the Griepink et al. [10] isolated and identified the sex pheromone components from the female moth′s gland. The main chemical components of the sex pheromones of *Symmetrischema tangolias* are (3*E*,7*Z*)-tetradecadienyl acetate and *E*-3-tetradecenyl acetate, which were identified in the pheromone in the ratio 2:1, while Ragoussis et al., effectively investigated the synthesis of (3*E*,7*Z*)-tetradecadienyl acetate with the help of the Wittig and Knoevenagel reactions [13].

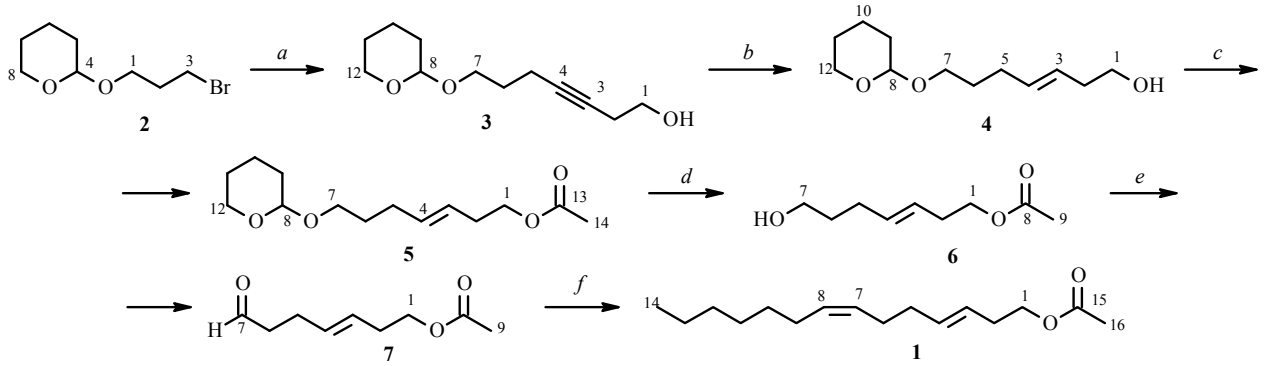
It is a very challenging task to synthesize sex pheromones stereoselectively and stereospecifically with a high overall yield and enhanced isomeric purity using a simple method. To enhance the isomeric purity and overall yield, our research group tried to address the economical, highly efficient stereoselective synthesis of (3*E*,7*Z*)-tetradecadienyl acetate. This is achieved by using stereospecific reduction and the Wittig reaction at key stages with a simple base to get stereospecific (*E*,*Z*) isomeric purity of the pheromone (**1**) in 99% yield by GC.

(3*E*,7*Z*)-Tetradecadienyl acetate (**1**), the core constituent of the pheromone of *Symmetrischema tangolias,* was synthesized by a stereoselective and stereospecific method, as mentioned. This method consists of six experimental steps (Scheme 1).

At the initial stage, to eliminate the terminal alcoholic group on both sides, a well-established protection reaction of 3-bromo-1-propanol was carried out by the reported method, which gives 2-(3-bromopropoxy)-tetrahydro-2*H*-pyran (**2**). It was employed as a starting material. Further, an alkylation is carried out with 3-butynol using $LiNH_2$ in liquid NH_3 to afford 7-(tetrahydro-2*H*-pyran-2-yloxy)hept-3-yn-1-ol (**3**) with 85% yield. An (*E*)-allylic bond exists in the targeted molecule; hence, to access this (*E*)-allylic bond, we further carried out a stereospecific and stereoselective reduction of the alcohol to the corresponding 7-(tetrahydro-2*H*-pyran-2-yloxy)hept-3-en-1-ol (**4**) in the presence of $LiAlH_4$ in diglyme, obtaining a good yield (84%) under heating conditions. The (*E*)-allylic bond in compound **4** was confirmed by gas chromatography (GC), indicating that it was predominant at retention time 8.511 with 98% purity.

TABLE 1. **Green Metrics Calculations**

Particulars	MI	%RME	%CE	%AE	Yield, %
Step I	8.76	11.4	79.65	72.40	62
Step II	6.59	15.17	83.85	85.64	84
Step III	4.80	20.82	93.24	87.54	80
Step IV	3.2	31.21	59.8	67.18	86
Step V	29.52	3.38	60.7	98.82	60
Step VI	34.08	2.93	15.24	41.26	35



a. 3-Butynol, $LiNH_2$, liq. NH_3, –78°C; *b*. LAH, diglyme, 140°C; *c*. CH_3COCl, pyridine, 0°C, DCM; *d*. *p*-TSA, r.t., DCM; *e*. PCC, 0°C, DCM; *f*. PTB, Wittig salt, –78°C, THF

Scheme 1.

The resulting alcohol **4** was then acylated by using acetyl chloride and pyridine in dichloromethane to give the 7-(tetrahydro-2*H*-pyran-2-yloxy)hept-3-en-1-yl acetate (**5**). It was purified by column chromatography using hexane–ethyl acetate in 9:1 ratio to give an 80% yield. Then the tetrahydropyranyl group was deprotected by using *p*-toluenesulfonic acid in methanol to give 7-hydroxyhept-3-en-1-yl acetate (**6**) in 78% yield. Compound **6** was oxidized subsequently in the presence of pyridinium chlorochromate (PCC) and sodium acetate in dichloromethane to give (3*E*)-7-oxohept-3-en-1-yl acetate (**7**) in 60% yield. Wittig olefination of (3*E*)-7-oxohept-3-en-1-yl acetate (**7**) was carried out with *n*-heptyltriphenylphosphonium bromide in the presence of potassium tertiary butoxide in THF at –78°C to produce the (*Z*)-stereoselectivity with 99% isomeric purity of the targeted molecule (3*E*,7*Z*)-tetradecadienyl acetate (**1**) in 35% yield. The stereochemical properties obtained by the Wittig reaction due to saturated aliphatic nonstabilized triphenylphosphonium ylides when reacted with primary aliphatic aldehydes in nonpolar solvents (such as THF) at –78°C in the absence of free salt led to primarily (*Z*)-olefins.

The target molecule was confirmed on the basis of spectroscopic data. All the spectral data, IR, ^{1}H NMR, ^{13}C NMR, and DEPT, showed good agreement with the corresponding pheromone structure (3*E*,7*Z*)-tetradecadienyl acetate (**1**), while the GC report shows 99% (*E*,*Z*) isomeric purity. Finally, all the products of each step were confirmed by mass spectrometry.

Synthesis of sex pheromones is a multistep process, and it is a challenging task to follow green chemistry principles. The green metrics have been considered as an evaluator of environmental sustainability in diminishing the amount of theoretical waste. The green metrics consist of parameters like mass intensity (MI), reaction mass efficiency (RME), carbon efficiency (CE), and atom economy (AE). The MI stands for yield stoichiometry, and the RME stands for yield and excess catalytic amount of reactant excluding solvent. The CE shows the gain or loss of carbon atoms in the conversion of reactant to product, and finally AE gives provides a theoretical calculation of the process and environmental efficiency. The standard values of green metrics under ideal conditions are MI ≈ 1%, RME ≈ 100%, %CE ≈ 100, and %AE ≈ 100. To explain the greenness of the present synthesis, we have studied green metrics calculations [14].

The greater yields of the product indicate that significant RME values and moderate yield generate moderate RME values. Furthermore, the percent CE of step 1 is 79.65%, while at step 6 the percent CE is 15.24%, demonstrating a remarkable conversion. Finally, the percent atom economy of step 1 is 72.40%, and that at step 6 is 41.26%, indicating maximum conversion of starting materials into product and minimum waste.

EXPERIMENTAL

General. All chemicals used were purchased from Sigma-Aldrich and used as such. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 (δ 2.5) on a Bruker instrument (300 MHz, 400 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR) using TMS as an internal standard. IR spectra (KBr) were recorded on a Bruker FT-IR spectrometer, in cm^{-1}.

Gas chromatography-mass spectrometric (GC-MS) analyses were carried out on a Hewlett-Packard 5890-5970 system, equipped with a SPB-1 capillary column (20 m × 0.25 mm, 0.33 μm film thickness, Supelco, Sigma-Aldrich Ltd., Greece): carrier gas, helium, 1 mL/min; injector temperature, 230°C;

oven temperature, 50°C for 5 min isothermal and then raised to 250°C at a rate of 4°C/min and then held for 10 min; ion source temperature, 220°C; interface temperature, 250°C; mass range, 40–500 amu; EI, 70 eV. GC analyses were carried out on an Agilent 6890 N chromatograph either in a polar capillary column CP-Wax 52 CB (30 m × 0.32 mm, 0.25 μm film thickness, Varian Inc., CA) or in a nonpolar capillary column SPB1 (20 m × 0.32 mm, 1.0 μm film thickness, Supelco, Sigma-Aldrich Ltd.): carrier gas, helium, 1 mL/min; injector temperature, 200°C; oven temperature, 60°C for 5 min isothermal and then raised to 250°C at a rate of 4°C/min and then held for 15 min.

Thin-layer chromatography (TLC) was performed on 0.25 mm precoated silica gel 60 F 254 glass plates, and column chromatography on silica gel, 60–120 mesh size (Merck & Co., Darmstadt, Germany). All commercial reagents and solvents were used as supplied. All reactions of air- and water-sensitive materials were run in oven-dried glassware under nitrogen. Air-sensitive solutions or liquids were transferred with glass syringes. Wittig salt *n*-heptyltriphenylphosphonium bromide was prepared by treatment of 1-bromoheptane with triphenyl phosphine in acetonitrile. Tetrahydrofuran was distilled from sodium benzophenone ketyl.

7-(2-Tetrahydropyranyloxy)-hept-3-yn-1-ol (3). About 500 mL ammonia was collected in a 2 L three-neck reaction flask attached to an ammonia condenser; to that, 1 g ferric nitrate and Li metal (8 g, 1121 mmol) were added portionwise. After 45 min, 3-butyn-1-ol (41 mL, 538 mmol) was added dropwise. Half an hour later, 3-bromopropanol – OTHP 2 (100 g, 448 mmol), HMPA (20 mL), and THF (200 mL) were added in 1 h. Then the reaction was maintained for 2 h, and the ammonia was allowed to evaporate. The reaction mixture was quenched with solid ammonium chloride (50 g) and saturated ammonium chloride solution (100 mL). The reaction mixture was extracted with diethyl ether (1 L) and washed with water (3 × 100 mL), followed by saturated sodium chloride solution (50 mL). Then sodium sulfate (50 g) was added, and the crude product was concentrated and then purified by column chromatography to give alkylated product **3** as a colorless oil, 81 g (85%). IR (KBr, ν_{max}, cm^{-1}): 2938.9 (CH), 3438 (OH). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.64–1.43 (4H, m, $2CH_2$), 1.73–1.64 (4H, m, $2CH_2$), 2.20–2.15 (2H, m, CH_2), 2.32–2.27 (2H, m, CH_2), 3.0 (1H, br.s, OH), 3.42–3.35 (2H, m, CH_2), 3.57–3.52 (2H, s, CH_2), 3.79–3.67 (2H, m, CH_2), 4.95 (1H, s, CH). GC-MS (Purity) = 99.04%. Observed GC-MS *m/z* 211.1 $[M-1]^-$ (calcd for $C_{12}H_{20}O_3$, 212.28).

7-(2-Tetrahydropyranyloxy)-hept-3(*E*)-en-1-ol (4). Enynol **3** (100 g, 471 mmol) was added slowly with stirring to an ice-cold solution of lithium aluminum hydride (35.79 g, 943 mmol) in diglyme (450 mL). After heating for 1 h at 140°C, the mixture was decomposed by careful dropwise addition of cold water (2 mL) and 6 M sodium hydroxide (25 mL). The solution was then filtered, and the solid was washed with diethyl ether (5 × 100 mL). Then the combined filtrate was washed with brine (50 mL) and dried with sodium sulfate (20 g). The reaction mixture was concentrated, and the residual oil was purified by column chromatography to give the product as a colorless liquid **4** (85 g, 84%). IR (KBr, ν_{max}, cm^{-1}): 2937 (CH), 1642 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 5.51–5.31 (2H, m, 2CH), 4.5 (1H, br.s, OH), 3.83–3.64 (2H, m, CH_2), 3.56–3.52 (2H, m, CH_2), 3.46–3.32 (2H, m, CH_2), 2.59 (2H, s, CH_2), 2.22–2.16 (3H, m, CH_2), 2.09–2.02 (2H, m, CH_2), 1.78–1.54 (6H, m, $3CH_2$). GC (Purity) = 98.05%. Observed GC-MS *m/z* 214.2 $[M]^+$ (calcd for $C_{12}H_{22}O_3$, 214.30).

7-(2-Tetrahydropyranyloxy)-hept-3(*E*)-enl Acetate (5). To a solution of alcohol **4** (50 g, 23 mmol), dichloromethane (100 mL) and pyridine (24.5 mL, 303 mmol) were added in one portion. and the mixture was cooled to 0°C. Then acetyl chloride (20 mL, 280 mmol) was added slowly along with dichloromethane (20 mL). The reaction mixture was poured onto ice, and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL) and brine (10 mL) and then dried with sodium sulfate (20 g). Removal of the solvent and purification of the residue by column chromatography yielded acetate **5** as a colorless oil (48 g, 80%). IR (KBr, ν_{max}, cm^{-1}): 1738 (C=O), 2939 (CH). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.50–1.97 (5H, m, CH_2, CH_3), 1.98–2.02 (8H, m, $4CH_2$), 2.17–2.26 (2H, q, CH_2), 3.25–3.43 (2H, m, CH_2), 3.61–3.77 (2H, m, CH_2), 3.92–4.00 (2H, m, CH_2), 4.47–4.50 (1H, m, CH), 5.27–5.48 (2H, m, 2CH), GC (Purity) = 92.84%. Observed GC-MS *m/z* 256.2 $[M]^+$ (calcd for $C_{14}H_{24}O_4$, 256.33).

7-Hydroxyhepta-3(*E*)-enyl Acetate (6). A solution of protected acetate **5** (40 g), 4-toluene-sulfonic acid (0.5 g), and methanol (50 mL) was stirred for half an hour at room temperature. A solution of 5% sodium bicarbonate (5 mL) was added to the reaction mixture, and the solvent was removed. The residue was extracted with diethyl ether (3 × 100 mL), and the combined ether extracts were washed with brine (20 mL) and dried with sodium sulfate (20 g). The solution was evaporated *in vacuo*, and the residue was subjected to column chromatography to give hydroxy acetate **6** as a colorless oil (25 g, 78%). IR (KBr, ν_{max}, cm^{-1}): 1642 (C=C), 1737 (C=O), 2936 (CH), 3626 (OH). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.56–1.69 (2H, m, H-6), 2.01–2.15 (5H, m, CH_3 2H-5), 2.25–2.40 (3H, m, HO 2H-2), 3.62 (2H, t, H-7), 4.07 (2H, t, H-1), 5.35–5.61 (2H, m,H-3, 4). GC (Purity) = 96.08%. Observed GC-MS *m/z* 112 $[M-60]^+$ (calcd for $C_9H_{16}O_3$, 172.22).

7-(Acetoxy)hepta-3(*E*)-enal (7). Pyridinium chlorochromate (37 g, 174 mmol) and sodium acetate (4.7 g, 58 mmol) were suspended in anhydrous dichloromethane (200 mL) and cooled to 0°C. Then the alcohol **6** (20 g, 116 mmol) in dichloromethane (20 mL) was added in one portion to the mechanically stirred solution. After 15 min the cooling bath was removed and the resultant mixture stirred for 2 h at room temperature. It was diluted with dry diethyl ether (50 mL) and filtered through a pad of Celite. The filtrate was concentrated in vacuum to give the corresponding crude aldehyde, which was subjected to column chromatography to give aldehyde **7** as a colorless liquid (12 g, 60 %). IR (KBr, ν_{max}, cm^{-1}): 1642 (C=C), 1727 (C=O), 2951 (CH). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.04 (3H, s, $\underline{CH_3}$), 2.31–2.36 (4H, m, 2H-5, 2H-2), 2.36–2.52, (2H, t, 2H-6), 4.05–4.08 (2H, t, H-2), 5.47–5.51 (2H, m, H-3, 4), 9.76 (1H, t, $\underline{CHO}$).

GC (Purity) = 94.88%. Observed GC-MS *m/z* 142 $[M - 28]^+$ (calcd for $C_9H_{14}O_3$, 170.20).

(3*E*,7*Z*)-3,7-Tetradecadienyl Acetate (1). The aldehyde **7** (8.67 g, 504 mmol) was dissolved in THF (20 mL) and slowly added to a stirred and cooled (–78°C) freshly prepared solution of the *n*-heptylidenetriphenylphosphorane [prepared by addition of a solution of potassium tertiary butoxide (12.69 g, 113 mmol) to a suspension of *n*-heptyltriphenylphosphonium bromide (25 g, 566 mmol) in THF (100 mL)]. After the addition, the reaction mixture was stirred for 1 h at the same temperature and then brought to room temperature while stirring. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) and diluted with diethyl ether (100 mL). Then it was washed with water (3 × 50 mL) and brine (20 mL) and dried over sodium sulfate (20 g). Subsequent evaporation of the solvent under vacuum and column chromatography afforded the pure pheromone acetate **1** as a colorless oil 4.5 g (35%). IR (KBr, ν_{max}, cm^{-1}): 1658 (C=C), 1741 (C=O), 2923 (CH). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87–0.90 (3H, t, J = 6.9, H-14), 1.27–1.30 (8H, m, 4 × CH_2), 2.02–2.08 (9H, m, $\underline{CH_3}$-CO- and 4 × CH_2), 2.31–2.32 (2H, q, H-2), 4.05–4.08 (2H, t, J = 6.9, H-1), 5.35–5.36 (4H, m, H-3, 4, 7, 8). ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm): 13.94, 20.65, 22.56, 27.01, 28.89, 27.16, 29.58, 31.70, 31.88, 32.62, 63.86, 125.36, 128.67, 130.20, 132.71, 170.56. ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 20.64, 22.55, 126.66, 127.48, 128.85, 129.24, 130.74. GC (Purity) = 95.56%. Observed GC-MS *m/z* 252.2 $[M]^+$ (calcd 252.39).

In summary, cheap and commercially available 3-bromo-1-propanol is a very useful reagent for the preparation of pheromone (3*E*,7*Z*)-tetradecadienyl acetate (**1**), the main pheromone component of the potato tuber moth *S. tangolias* (Gyen). It was synthesized in six steps, and the products can be easily purified by column chromatography. The steps involved are simple, highly stereoselective, and cost effective, and the procedures easily scalable, which makes this method useful in producing the pheromone for the control of the serious insect pest *Symmetrischema tangolias.*

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