A Versatile Approach for the Synthesis of (11*Z*, 13*Z*)-hexadecadien-1-yl Acetate and (13*Z*)-hexadecen-11-ynyl Acetate: Main Sex Pheromone Components of the Processionary Moths *Thaumetopoea Processionea* and *Thaumetopoea Pityocampa*

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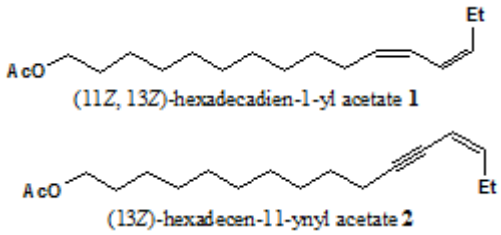
A versatile approach for the synthesis of (11Z, 13Z)-hexadecadien-1-yl acetate and (13Z)-hexadecen-11-ynyl acetate is described using cross-coupling reactions in the key steps. These compounds are major components of the sex pheromone of the oak processionary moth Thaumetopoea processionea and the pine processionary moth Thaumetopoea pityocampa respectively. The very simple, efficient, and practical method described herein provides a generally synthetic approach to other (Z, Z)-diene compounds.

Keywords: (11Z, 13Z)-hexadecadien-1-yl acetate; (13Z)-hexadecen-11-ynyl acetate; cross-coupling reactions; sex pheromone

The oak processionary moth *Thaumetopoea processionea* L. (Lepidoptera, Thaumetopoidae) is a serious pest of the oak trees (*Quercus robur* L., *Quercus cerris* L.) in many areas of western, southern and central Europe. It is usually found at the forest edges or in open spaces, such as parkland, forming communal nests on the trunks of oak trees, feeding on their foliage. Apart from its impact on plant health, *T. processionea* also poses a public health problem because the larvae are covered by minute urticating hairs which contain a toxin, and contact with these can cause severe and persistent skin irritations, eye problems, sore throats and respiratory problems[1]. *Thaumetopoea pityocampa* is a pest of *Pinus*, *Cedrus* and *Larix* in the Mediterranean and North Africa. It is present throughout the littoral zone and warmer regions, and can be found in the interior of the continent at sites where the climatic and site conditions are suitable.

T. pityocampa's dependence on relatively high temperatures has limited its northern spread, and it appears unable to survive lower winter temperatures. The caterpillars cause severe damage to pine plantations, especially in warm districts and low altitudes. Young pine plantations are the most susceptible, and may be completely destroyed if the attack is severe enough [2].

(11*Z*, 13*Z*)-Hexadecadien-1-yl acetate **1** has been identified in female pheromone gland extracts of *T. processionea* by Frérot and Demolin [3]. Quero et.al.[4] confirm that (11*Z*, 13*Z*)-hexadeca-dien-1-yl acetate **1** is the major pheromone component found in female gland extracts. The biological activity of synthetic **1** was evaluated in field trials by Breuer et. al. [5]. The main component of the sex pheromone of the female *T. pityocampa* was isolated and identified as (13*Z*)-hexadecen-11-ynyl acetate **2** by Guerrero et. al. [6]. Since 1981, the syntheses of **1** and **2** have been reported by several groups, employing different procedures for the construction of the enyne and diene moiety [7-16].



Recently, D. T. Williams et. al.[17] have demonstrated, that the positioning of the pheromone trap in the tree canopy, the design of the trap, and the source of the pheromone lure all together influence the number of adult male oak processionary moths caught in pheromone traps. All these factors need to be taken into consideration when designing a standardized monitoring program for this significant insect pest.

In this paper, we report a new versatile stereoselective approach for the synthesis of **1** and **2** from cheap and readily available starting materials using cross-coupling reactions for the stereospecific introduction of double bonds.

Experimental part

^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker Avance 300 MHz spectrometer in $CDCl_3$, using the solvent line as reference. EI-MS (70 eV) mass spectra were recorded on Hewlett-Packard 5972 GC-MS instrument and on GS-MS System Agilent Technologies with Triple-Axis Detector 2007. HRMS in APCI mode ionization were recorded with an LTQ XL Thermo Scientific mass spectrometer for the key and desired compounds.

All air-sensitive reactions were carried out in inert atmosphere under argon. The solvents were dried according to standard procedures. Pd catalysts were prepared as described in the literature. GC column (phenylmethylsiloxane): HP-5MS (30 m x 0.25 mm x 0.25 μm). Column chromatography: silica gel (Merck, Darmstadt), mesh 70-230. Thin layer chromatography

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(TLC): silica gel layered aluminum foil (60 F_{254} Merck, Darmstadt). All other chemicals were used as purchased.

The experimental procedures for the synthesis of the key compounds **7** and **8** and the target compounds **1** and **2** are given below. The spectral data of compounds **4, 5** and **6** were in excellent agreement with those previously reported [19, 21, 22].

(Z)-14-tert-butoxy-1-chlorotetradec-1-en-3-yne 7

A mixture of $Pd(PPh_3)_4$ (5 mol%, 0.4 mmol, 0.48g), (*Z*)-1,2-dichloroethene (25.2 mmol, 2.44 g), 12-(*tert*-Butoxy)-dodec-1-yne **6** (8.4 mmol, 2 g) and *n*-$BuNH_2$ (16.8 mmol, 1.22 g) in anhydrous benzene (40 mL) was stirred for 15 min. at room temperature under argon atmosphere and CuI (10 mol%, 0.8 mmol, 160 mg) was then added. The stirring was continued until TLC analysis indicated complete consumption of the alkyne. The reaction mixture was diluted with benzene and treated with saturated aqueous solution of $NaHCO_3$ and then with brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed in vacuum. The crude product was purified by column chromatography using petroleum ether/diethyl ether, 20:1 as eluent, to yield the desired chloroenyne **7** (1.5 g, 5.0 mmol, 60%). Elemental analysis: Calculated for $C_{18}H_{31}ClO$: C, 72.33%; H, 10.45%; Cl, 11.86%. Found: C, 72.39%; H, 10.37; Cl, 11.83%. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.28 (d, *J* = 7.2 Hz, 1H), 5.85 (dt, *J* = 7.2, *J* = 2.1 Hz, 1H), 3.31 (t, *J* = 6.7 Hz, 2 H), 2.38 (td, *J* = 6.9, *J* = 2.1 Hz, 2H), 1.63-1.28 (m, 16 H), 1.2 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ126.67, 112.50, 99.43, 74.58, 72.37, 61.62, 30.68, 29.53, 29.48, 29.43, 29.07, 28.77, 28.46, 27.55, 26.21, 19.64; GC: t_r = 26.31, 99%; MS(EI) (*m/z*): 283 (5%), 206 (2%), 141 (6%), 119 (12%), 105 (27%), 91 (27%), 59 (71%), 57 (100%), 29 (16%); APCI (+)-HRMS: calcd. for $C_{18}H_{31}ClO$ $[M + H]^+$: 299.2136, found: 299.2135.

(Z)-16-tert-butoxyhexadec-3-en-5-yne 8

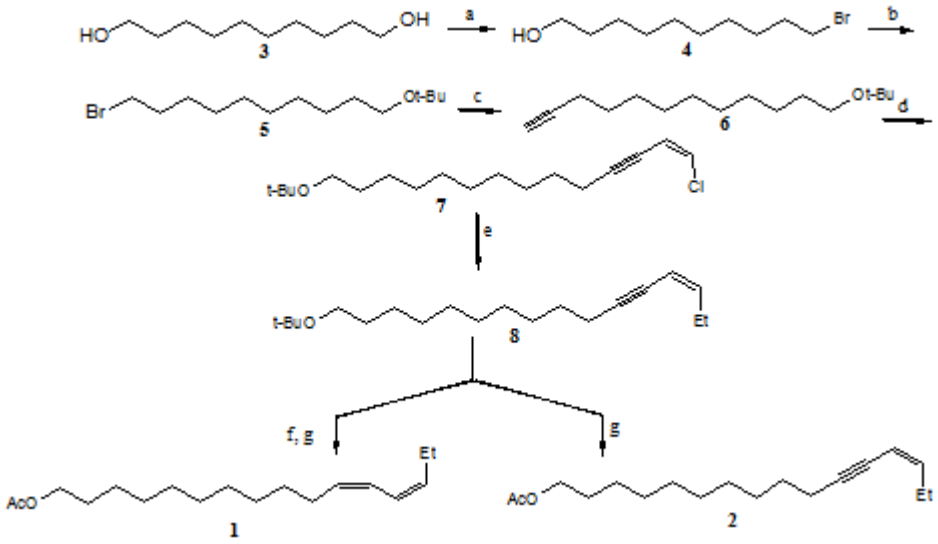
To a solution of **7** (5.0 mmol, 1.5 g) and 3 mol% $FeCl_3$ (0.024 g) in a mixture of THF (10 mL) and DMPU (1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) (10 mL) was added dropwise (over 10 min.) a 1.0 M solution of ethylmagnesium bromide in THF (10.4 mL) at room temperature. Stirring was continued until all the starting material has been consumed. The reaction mixture was hydrolyzed at 0 °C with aqueous 1 M HCl. After separation of the phases, the aqueous layer was extracted with Et_2O (2 x 50 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum and the crude product was purified by column chromatography using petroleum ether/diethyl ether, 40:1 as eluent, to yield the desired enyne **8** (1.16 g, 3.97 mmol, 80%). Elemental analysis: Calculated for $C_{20}H_{36}O$: C, 82.12%; H, 12.41. Found: C, 82.19%; H, 12.37. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.80 (dt, *J* =10.5 Hz, *J* = 6.0 Hz, 1H), 5.40 (dt, *J* = 10.5 Hz, *J* = 1.4 Hz, 1H), 3.31 (t, *J* = 6.7 Hz, 2H), 2.35-2.24 (m, 4H), 1.60-1.28 (m, 16H), 1.18 (s, 9H), 1.0 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.07, 108.68, 94.52, 77.17, 72.39, 61.64, 30.69, 29.56, 29.51, 29.48, 29.12, 28.85, 27.56, 26.23, 23.41, 19.51, 13.45; GC: t_r = 21.67, 98.5%; MS(EI) (*m/z*): 292 (0.5%), 277 (2%), 150 (10%), 135 (10%), 121 (8%), 107 (10%), 94 (51), 79 (26%), 57 (100%), 41 (18%); APCI (+)-HRMS: calcd. for $C_{20}H_{36}O$ $[M + H]^+$: 293.2839, found: 293.2839.

(11Z, 13Z)-Hexadecadien-1-yl acetate 1

A solution of cyclohexene (0.67 g, 8.2 mmol) in THF (3 mL) was added dropwise to a solution of BH_3-dimethtylsulfide complex (4.1 mmol, 0.312 g) in THF (5 mL) at 0 °C under argon. The reaction mixture was stirred for 2 h between –10 and 0 °C, then allowed to warm to room temperature and stirred for 1.5 h. The white resulting slurry of dicyclohexylborane was cooled back to 0°C and a solution of (*Z*)-16-*tert*-butoxyhexadec-3-en-5-yne **8** (0.8 g, 2.74 mmol) in 1.5 mL THF was added dropwise over 20 min. The resulting mixture was stirred for 2 h at 0 °C and then allowed to warm to 20 °C and stirred overnight. The reaction mixture was cooled to 0 °C, glacial acetic acid (1.6 mL) was added and the mixture was warmed to room temperature and stirred overnight. The solution was diluted with Et_2O (50 mL), washed with saturated aqueous solution of $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum and the resulting residue was purified by flash chromatography using petroleum ether/diethyl ether, 40:1 as eluent, to yield the crude diene (0.7 g, 2.38 mmol, 87 %). GC-MS analysis: t_r =22.32, 75% (chemical purity). This was directly converted into the corresponding acetate **1** by treatment with $FeCl_3$ (36 mg) and acetic anhydride (2.4 mL) in diethyl ether (15 mL). The resulting dark brown solution was stirred for 20 h at room temperature. A saturated aqueous solution of Na_2HPO_4 (10 mL) was added and the mixture was stirred for 2 h. The solid $FePO_4$ was filtered off and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The collected organic phases were dried over anhydrous $MgSO_4$ and then concentrated in vacuum. The red oily residue was purified by column chromatography using *n*-hexane/diethyl ether, 10:1 as eluent, to yield (11*Z*, 13*Z*)-hexadecadien-1-yl acetate **1** (0.51 g, 1.8 mmol, 78%, isomeric purity 95.74%). Elemental analysis: Calculated for $C_{18}H_{32}O_2$: C, 77.09%; H, 11.50%. Found: C, 77.17%; H, 11.44%. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.28-6.16 (m, 2H), 5.47-5.39 (m, 2H), 4.04 (t, *J* = 7.5 Hz, 2 H), 2.25-2.12 (m, 4H), 2.03 (s, 3H), 1.63-1.56 (m, 2H), 1.26 (m, 14H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.13, 133.50, 132.02, 123.37, 122.94, 64.57, 29.57, 29.43 (2C), 29.41, 29.20, 29.18, 28.53, 27.39, 25.84, 20.93, 20.71, 14.14; GC: t_r = 22.05, 95.74%; MS(EI) (*m/z*): 280 (15%), 149 (8%), 135 (16%), 121 (23%), 109 (17%), 95 (58%), 82 (66%), 67 (100%), 55 (33%), 43 (43%); APCI (+)-HRMS: calcd. for $C_{18}H_{32}O_2$ $[M + H]^+$: 281.2475, found: 281.2473. The spectral data of **1** are in excellent agreement with those previously reported [27].

(13Z)-hexadecen-11-ynyl acetate 2

To a solution of **8** (0.36 g, 1.23 mmol) in diethyl ether (10 mL), acetic anhydride (1.4 mL) was added and then anhydrous $FeCl_3$ (22 mg, 0.13 mmol). The dark brown solution was stirred for 20 h at room temperature. A saturated aqueous solution of Na_2HPO_4 (10 mL) was added, and the mixture was stirred for 2 h. The solid $FePO_4$ was filtered off, and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The collected organic phases were dried over anhydrous $MgSO_4$, and then concentrated in vacuum. The red oily residue was purified by column chromatography using *n*-hexane/diethyl ether, 10:1 as eluent, to yield (13*Z*)-hexadecen-11-ynyl acetate **2** (0.26 g, 0.9 mmol, 76%, isomeric purity 99%). Elemental analysis: Calculated for $C_{18}H_{30}O_2$: C, 77.65%; H, 10.86%. Found: C, 77.57%; H, 10.91%. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.84-5.76 (m, 1H), 5.42-5.38 (m, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 2.35-2.22 (m, 4H), 2.04(s, 3H), 1.61-1.51 (m, 4H), 1.28 (bs, 12 H), 1.0 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.24, 144.05, 108.67, 94.45, 77.17, 64.62, 29.41, 29.40, 29,20, 29.06, 28.81 (2C), 28.55, 25.87, 23.39, 21.00, 19.48, 13.43; GC: t_r = 26.12, 96% (chemical purity); MS(EI) (*m/z*): 278 (1%), 135 (6%), 119 (13%), 105 (21%), 79 (100%),



Scheme 1. *Reagents and conditions*: (a) HBr 47% aq., toluene, reflux; (b) MTBE, H_2SO_4 cat., 40°C; (c) LiC≡CH·$NH_2C_2H_4NH_2$, DMSO, 0°→r.t., 6h; (d) *cis*-1,2-dichloroethylene (4 eq.), 5 mol% $PdCl_2(PPh_3)_2$, *n*-$BuNH_2$ (2 eq.), 10 mol% CuI, benzene, r.t.; (e) EtMgBr (2 eq.), 3 mol% $FeCl_3$, THF:DMPU = 1:1, r.t.; (f) Cy_2BH, THF, 0°→t., CH_3COOH, 0°→r.t.; (g) $FeCl_3$, $(C_2H_6O)_2O$, Et_2O, r.t..

67 (22%), 43 (99%), 29 (11%). APCI (+)-HRMS: calcd. for $C_{18}H_{30}O_2$ $[M + H]^+$: 279.2319, found 279.2318. The spectral data of **2** are in excellent agreement with those previously reported [8,15].

Results and discussions

The synthesis of (11*Z*, 13*Z*)-hexadecadien-1-yl acetate **1** and (13*Z*)-hexadecen-11-ynyl acetate **2** (Scheme1) starts with the monobromination [18, 19] of 1, 10-decanediol **3** to yield in 80% 10-bromodecan-1-ol **4**, which was subsequently protected with MTBE (methyl-*t*-butyl ether) to give 1-bromo-10-(*tert*-butoxy)-decane **5** in 75% yield after purification [20, 21].

The protected alcohol **5** was further reacted with lithium acetylide – ethylenediamine complex to give 12-(*tert*-butoxy)-dodec-1-yne[21,22] **6** in 85% yield. The stereospecific introduction of the double bond, for the construction of the enyne moiety was achieved by the methodology based on the Pd(0)-catalyzed cross-coupling reaction between terminal alkynes and haloalkenes.[23,24] Thus, the cross-coupling reaction of alkyne **6** with (*Z*)-1,2-dichloroethene in the presence of 5 mol % $PdCl_2(PPh_3)_2$, 10 mol % CuI and *n*-$BuNH_2$ afforded the (*Z*)-chloroenyne derivative **7** in good yield (60%) and high isomeric purity > 99% from GC analysis. The *Z*-configuration of chloroenyne **7** was confirmed by ^{1}H NMR which showed a doublet at 6.2 ppm with ^3J = 7.2 Hz (the *cis* coupling constant) and a doublet of triplets at 5.8 ppm with ^3J = 7.2 Hz, ^5J = 2.1 Hz, respectively. Further, for the construction of the entire skeleton of the pheromones **1** and **2**, the iron-catalyzed alkenylation of organomagnesium compounds was take into consideration.[25] Reaction of ethylmagnesium bromide with (*Z*)-chloroenyne **7** in the presence of 3 mol % $FeCl_3$ in THF-DMPU (1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) as solvent afforded (*Z*)-16-(*tert*-butoxy)-hexadec-3-en-5-yne **8** in high yield (80%) and isomeric purity > 99% from GC analysis. The *Z*-configuration of ethylenyne **8** was also confirmed by ^{1}H NMR which showed a doublet of triplets at 5.80 ppm with ^3J =10.5 Hz (the *cis* coupling constant) and ^3J = 6.0 Hz, and a doublet of triplets at 5.40 ppm with ^3J = 10.5 Hz and ^5J = 1.4 Hz, respectively. The selective hydroboration[26] of the triple bond in enyne **8** with dicyclohexylborane and successive protonolysis of the vinyl-boron intermediate with acetic acid gave the desired (*Z, Z*)-diene. The resulting diene and compound **8** were directly converted into the corresponding acetates **1** and **2** by treatment with $FeCl_3$ and acetic anhydride in diethyl ether to afford the desired compounds in 78% and 76% yield. The overall yield of the target products was 18% for compound **1** and 20% for compound **2**. The ^{1}H NMR, ^{13}C NMR, and MS data for the synthetic pheromones **1** and **2** were in excellent agreement with those reported previously.[8,15,27] The purity of **1** and **2** was analyzed by GC-MS. The sample of compound **1** consisted of 95.74% of (11Z, 13Z)-**1**, 1.41% of its (11*Z*, 13*E*)-isomer, 1.93% of (11*E*, 13*Z*)-isomer and 0.92% (11*E*, 13*E*)-isomer. The retention times for **1** and its isomers were assumed based on the literature data.[28] The isomeric purity for compound **2** was higher then 99% from the GC-MS analysis.

In summary, the work described herein establishes a versatile stereoselective approach to the synthesis of (11*Z*, 13*Z*)-hexadecadien-1-yl acetate **1** and (13*Z*)-hexadecen-11-ynyl acetate **2** the main sex pheromone components of the processionary moths *Thaumetopoea processionea* and *Thaumetopoea pityocampa*. The high yield and stereoselectivity, achieved using cross-coupling reaction in the key steps, in addition to the mild reaction conditions make the present process very useful in manufacturing the economically important pheromone lures against *T. processionea* and *T. pityocampa.*

In another paper was studied the synthesis of the monounsaturated sex pheromones of same lepidoptera involving mercury derivatives [29].

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