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Stereospecific Synthesis of (2*E*,13*Z*)-2,13-Octadecadienyl Acetate, the Sex Pheromone Component of the *Lepidoptera* Species

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Abstract: The main component of the sex pheromone of many lepidopteran pests, (2*E*,13*Z*)-2,13-octadecadienyl acetate (**1**), has been synthesized following a simple route using 12-(2-tetrahydropyranyloxy)-1-dodecyne (**2**) as the starting material.

Keywords: Attractant activity, hydroxymethylation, total synthesis, Wittig olefination

(2*E*,13*Z*)-2,13-Octadecadienyl acetate (**1**) has been identified as the major component of several sex pheromones of the female moth from family *Synanthedon* (*Sesiidae*)[1] and another serious pest of fruit trees, *Zeuzera pyrina L.* (*Cossidae*),[2] which belongs to the lepidopterous insect species. The first syntheses of the title compound by employing the acetylenic route using two alkylation steps of alkali metal 1-alkynylide with alkyl halide was achieved by Scharz and his colleagues.[1b] Since 1983, the syntheses of **1** have been reported by several groups.[2–9]

A new, alternative strategy for the synthesis of **1** (with part of carbon chain units C12 + C1 + C5) from cheap and readily available starting materials is described in this article. In an earlier communication,[10] the simple and practical method for obtaining 12-(2-tetrahydropyranyloxy)-1-dodecyne (**2**) was reported. This compound was employed as starting material in the synthesis of the target product **1** (Scheme 1).

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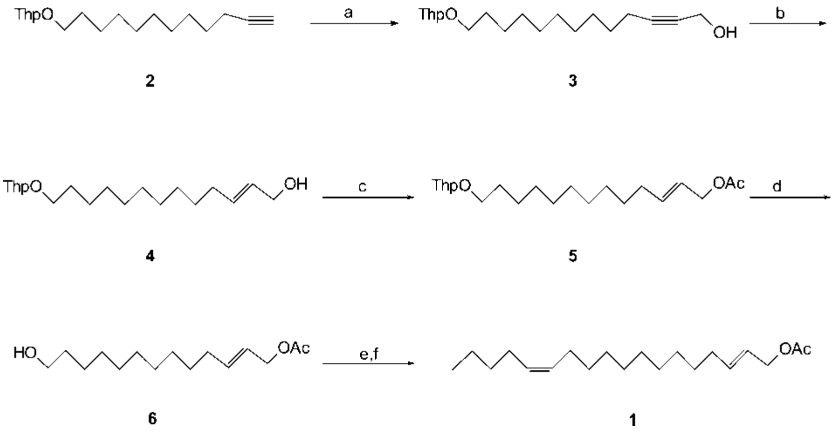

Scheme 1. Reagents and conditions: (a) i, EtMgBr, THF, 70 °C, 1 h. ii, $(CH_2O)_n$, 70 °C, 2 h; (b) $LiAlH_4$,THF, 70 °C, 2 h; (c) Ac_2O, pyridine, rt, 4 h; (d) p-TsOH, CH_3OH, 40 °C, 4.5 h; (e) PCC, CH_2Cl_2, rt, 1.5 h; (f) $CH_3CH_2CH_2CH_2CH{=}PPh_3$, THF, (−76 °C), 1 h.

Hydroxymethylation of the Grignard reagent of the terminal alkyne **2** (prepared by refluxing of **2** and of ethylmagnesium bromide in THF) with formaldehyde, which was generated in situ from paraformaldehyde,[11] afforded alcohol **3** in 71% yield.

To introduce the (*E*)-double bond present in **1**, the stereospecific reduction of propargyl alcohols to the corresponding (*E*)-allylic derivatives was performed.[12] In fact, **3** was stereoselectively converted in 84% to 2(*E*)-enol **4** on treatment with $LiALH_4$ in refluxing THF, and no traces of Z-isomer were detected by means of gas-liquid chromatography (GLC). The allylic alcohol **4** was then acetylated with acetic anhydride in pyridine to give the acetate **5**. Compound **5** was obtained in more than 90% yield after silica-gel chromatography and depyranylation, using of 4-toluenesulphonic acid (PTSA) in methanol, to give **6** in ~60% yield. The alcohol **6** was oxidized in dichloromethane with pyridinium chlorochromate (PCC)[13] to the corresponding aldehyde, which was used in the next step without purification. Crude aldehyde was converted to the final product via Wittig olefination with *n*-pentylidene-triphenylphosphorane. This reagent was prepared from *n*-pentyltriphenylphosphonium bromide[14] and sodium bis(trimethylsilyl)amide in refluxing THF. The olefination product was detected in 30% yield (from **6**) with highly (*Z*)-stereoselectivity (~ 98%). The geometry of the olefinic protons in acetate **1** was confirmed by ^1H NMR, which showed a multiplet at 5.35 with $J = 11.0$ Hz (the *cis* coupling constant was found by the homodecoupling technique) and two multiplets at δ 5.56 and 5.77 with $J = 15.3$ Hz (two protons from *trans* double bond).

In summary, the easily available 12-(2-tetrahydropyranyloxy)-1-dodecyne (**2**) is a very useful intermediate to the preparation of an acetate **1** in total synthesis.

EXPERIMENTAL

IR spectra were measured using a FT/IR-420 Jasco instrument (as film). ^{1}H NMR spectra were recorded with a Varian 200-MHz spectrometer for solutions in $CDCl_3$ (internal TMS). Spin–spin coupling constant (J) for olefinic protons from *cis* double bond of the final product was determined from carbon satellites using the homodecoupling technique on a Varian UnityPlus-500 instrument. MS spectra were measured on an API 365 spectrometer. Purity of the synthesized compounds was estimated by the GC method, using a Varian Star 3400 CX chromatograph; capillary column: DB1 (30 × 0.53 mm). Thin-layer chromatography was performed on Alufolien with silica gel 60 F_{254} (Merck). Flash column chromatography was carried out with 230–400-mesh silica gel (Merck, 0.04–0.063 mm).

All reactions of air- and water-sensitive materials were run in oven-dried glassware under argon. Air-sensitive solutions or liquids were transferred with glass syringes. *n*-Pentyltriphenylphosphonium bromide was prepared by treatment of 1-bromopentane with triphenyl phosphine in MeCN.[14] Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Paraformaldehyde was dried to constant mass in a vacuum desiccator over P_2O_5 at 0.1 mmHg for 4 days before use. All other chemicals were used as purchased.

13-(2-Tetrahydropyranyloxy)-2-tridecyn-1-ol (3). A solution of 12-(2-tetrahydropyranyloxy)-1-dodecyn (5.1 g, 19.2 mmol)[10] in THF (5 mL) at 5 °C was added to a solution of ethyl magnesium bromide, prepared from ethyl bromide (1.76 ml, 23.5 mmol) and magnesium turnings (0.52 g, 21.3 mmol) in THF (18 mL). The reaction mixture was refluxed for 1 h, then cooled to room temperature, and paraformaldehyde (0.8 g, 26.6 mmol) was added. The resultant mixture was refluxed with stirring for 2 h. The reaction was quenched with saturated NH_4Cl (25 mL) and extracted with hexane (3 × 50 mL), and the combined organic phases were washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and evaporated. Purification of the crude product by flash chromatography (eluent: hexane–ethyl acetate 2:1) gave **3** (4 g, 71%) as a colorless oil. IR: 3440 (O-H), 1022 (C–O); ^{1}H NMR: 1.20–1.96 (m, 23H, $11\mathbf{CH_2} + \mathrm{O}\mathbf{H}$), 2.14–2.28 (m, 2H, $\mathbf{CH_2}C{\equiv}CCH_2O$), 3.30–3.98 (m, 4H, $2OC\mathbf{H_2}$), 4.25 (t, 2H, $J = 2.2$, $C{\equiv}C\mathbf{H_2}O$), 4.58 (dd, 1H, $J = 2.6$, 4.2, $OC\mathbf{H}O$); HRMS (ESI): $[M + Na]^+$ m/e 319.2249, calcd. for $C_{18}H_{32}O_3Na$ 319.2244. The physical data of synthesized **3** were identical with those reported.[15]

13-(2-Tetrahydropyranyloxy)tridec-2(E)-en-1-ol (4). Lithium tetrahydridoaluminate (0.84 g, 22.1 mmol) was added slowly with stirring to an ice-cold solution of enynol **3** (3.36 g, 11.3 mmol) in THF (22 mL). After heating for 2 h at 70 °C, the mixture was decomposed by careful dropwise addition of cold water (0.9 mL), 6 M sodium hydroxide (0.7 mL), and water (2.7 mL). The solution was then filtered, the flask and precipitate were extracted with Et_2O (5 × 20 mL), and combined filtrates were washed with brine

(3 × 50 mL) and then dried with $MgSO_4$. The sample was concentrated, and the residual oil was flash chromatographed (eluent: hexane–ethyl acetate 2:1) to give **4** (2.83 g, 84%); IR: 3431 (O–H), 1028 (C–O), 965 (HC=CH)trans; ^{1}H NMR: 1.20–1.95 (m, 23H, 11$\mathbf{CH_2}$ + $\mathbf{OH}$), 1.96–2.14 (m, 2H, $\mathbf{CH_2}$CH=CHCH$_2$O), 3.30–3.96 (m, 4H, 2O$\mathbf{CH_2}$), 4.04–4.14 (m, 2H, C=$\mathbf{CH_2}$O), 4.58 (dd, 1H, J = 2.6, 4.2, OC**H**O), 5.54–5.80 (m, 2H, C**H**=C**H**); HRMS (ESI): $[M + Na]^+$ m/e 321.2418, calcd. for $C_{18}H_{34}O_3Na$ 321.2400. The physical data of synthesized **4** were identical with those reported.[15]

13-(2-Tetrahydropyranyloxy)tridec-2(E)-enyl acetate (5). A solution of acetic anhydride (1.63 g, 16 mmol) in pyridine (8 mL) was cooled in an ice bath. A solution of **4** (2.82 g, 9.5 mmol) in pyridine (3.6 mL) was added in one portion, and the mixture was stirred for 4 h while being warmed to room temperature. It was then poured onto a mixture of ice (ca. 40 g) plus hexane (25 mL), the mixture was shaken, and the phases separated. The aqueous layer was extracted with hexane (3 × 15 ml). The combined organic layers were washed with water and brine and then dried with $MgSO_4$. Removal of the solvent in vacuo and purification of the residue by flash chromatography (eluent: hexane–ethyl acetate 4:1) yielded acetate **5** as colorless oil (2.9 g, 90%) in 92% purity. IR: 1744 (C=O), 1030 (C–O), 970 (HC=CH) trans; ^{1}H NMR: 1.20–1.94 (m, 22H, 11$\mathbf{CH_2}$), 1.98–2.14 (m, 2H, $\mathbf{CH_2}$CH=CHCH$_2$O), 2.06 (s, 3H, CO$\mathbf{CH_3}$), 3.28–3.96 (m, 4H, 2O$\mathbf{CH_2}$), 4.51 (dd, 2H, J = 1.0, 6.4, $\mathbf{CH_2}$OAc), 4.57 (dd, 1H, J = 2.8 i 4.2, OC**H**O), 5.46–5.86 (m, 2H, C**H**=C**H**); HRMS (ESI): $[M + Na]^+$ m/e 363.2526, calcd. for $C_{20}H_{36}O_4Na$ 363.2506

13-Hydroxytridec-2(E)-enyl acetate (6). A solution of **5** (2.2 g, 6.5 mmol), 4-toluene-sulphonic acid (0.068 g, 0.3 mmol), and methanol was stirred for 4.5 h at 40 °C. A solution of 5% $NaHCO_3$ (1 mL) was added to the reaction mixture, and the sample was concentrated. The residue was extracted with Et_2O (3 × 20 mL), and the combined Et_2O extracts were washed with brine and dried with $MgSO_4$. The solution was evaporated in vacuo, and the residue was flash chromatographed (eluent: hexane–ethyl acetate 2:1) to give **6** as colorless oil (0.97 g, 58%). IR: 3439 (O–H), 1743 (C=O), 1026 (C–O), 968 (HC=CH) trans; ^{1}H NMR: 1.20–1.66 (m, 17H, 8$\mathbf{CH_2}$ + $\mathbf{OH}$), 1.98–2.14 (m, 2H, $\mathbf{CH_2}$CH=CHCH$_2$O), 2.06 (s, 3H, CO$\mathbf{CH_3}$), 3.64 (t, 2H, J = 6.6, $\mathbf{CH_2}$OH), 4.51 (dd, 2H, J = 0.8, 6.4, $\mathbf{CH_2}$OAc), 5.46–5.87 (m, 2H, C**H**=C**H**); MS (ESI): $[M + Na]^+$ m/e 279.20

(2E,13Z)-2,13-Octadecadienyl acetate (1). Pyridinium chlorochromate (0.67 g, 2.90 mmol) and sodium acetate (0.047 g, 0.6 mmol) were suspended in anhydrous CH_2Cl_2 (5 mL), and alcohol **6** (0.47 g, 1.85 mmol) in CH_2Cl_2 (3 mL) was added in one portion to the magnetically stirred solution. Then resultant mixture was stirred for 1.5 h at room temperature. It was diluted with dry Et_2O (20 mL), filtered through a pad of celite and neutral alumina, with the black gum being triturated in Et_2O. The filtrate was concentrated in vacuo to give the crude corresponding aldehyde. This aldehyde was dissolved in THF (0.8 mL) and slowly added to the stirred and cooled (−76 °C) freshly prepared solution of the *n*-pentylidenetriphenylphosphorane [prepared by addition a solution of sodium bis(trimethylsilyl)amide (0.41 g, 2.2 mmol) in THF (2 mL) to suspension of *n*-pentyl-triphenylphosphonium bromide (0.83 g, 2 mmol) in THF (3 mL) and heating under reflux for 40 min]. After the addition, the reaction mixture was stirred for 1 h at the same temperature and then left overnight at room temperature. Removal of the solvent furnished a residue, which was diluted with the mixture of hexane–ether 1:1 (10 mL), washed with water (5 mL), and dried over $MgSO_4$. A subsequent evaporation of the solvent and flash chromatography (eluent: hexane–ether 7:1) afforded 170 mg (30% yield from **6**) of the pure target compound, acetate **1**. IR: 1747 (C═O), 1024 (C–O), 968 (HC═CH) trans, 720 (HC═CH) cis; ^{1}H NMR: 0.89 (t, 3H, $J = 7.0$, **CH$_3$**), 1.20–1.46 (m, 18H, 9**CH$_2$**), 1.95–2.16 (m, 6H, 3**CH$_2$**CH═C), 2.06 (s, 3H, CO**CH$_3$**), 4.50 (dd, 2H, $J = 0.9$, 6.3, **CH$_2$**OAc), 5.35 (m, 2H, $J = 4.6$, 11.0, **CH═CH**), 5.57 (dtt, 1H, $J = 1.2$, 6.4, 15.3, **CH**═C), 5.75 (dt, 1H, $J = 6.5$, 15.3, **CH**═C); HRMS (ESI): $[M + Na]^+$ m/e 331.2623, calcd. for $C_{20}H_{36}O_2Na$ 331.2608. The spectral properties of **1** are in excellent agreement with those previously described.[4–8]

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