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STEREOSPECIFIC SYNTHESIS OF (*Z*)-13-HEXADECEN-11-YN-1-YL ACETATE

THE SEX PHEROMONE OF THE PROCESSIONARY MOTH, AND OF (5*Z*,7*E*)-5,7-DODECADIEN-1-OL, A SEX PHEROMONE COMPONENT OF THE FOREST TENT CATERPILLAR

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Abstract—(*Z*)-13-hexadecen-11-yn-1-yl acetate (**2**), the sex pheromone of *Thaumetopoea pytyocampa*, and (5*Z*,7*E*)-5,7-dodecadien-1-ol (**3**), a sex pheromone component of *Malacosoma disstria*, have been prepared in high chemical and stereoisomeric purity by synthetic schemes involving the stereospecific coupling of ω-functionalized 1-alkynes with (*Z*)- or (*E*)-1-iodo-1-alkenes in the presence of a catalytic amount of $(PPh_3)_4Pd$ and CuI, under phase transfer conditions.

Functionalized (*Z*)- or (*E*)-1,3-enynes of general formula **1** may be stereospecifically prepared in good yields by coupling reaction of ω-functionalized 1-alkynes with (*Z*)- or (*E*)-1-halo-1-alkenes in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium and cuprous iodide.[1] The reactions were carried out under phase transfer conditions employing benzyltriethylammonium chloride as phase transfer agent, an excess of 2.5N NaOH as base, and benzene as organic solvent.

$$R—\overset{Z\text{ or }E}{CH=CH}—C\equiv C—(CH_2)_n—Y$$

1

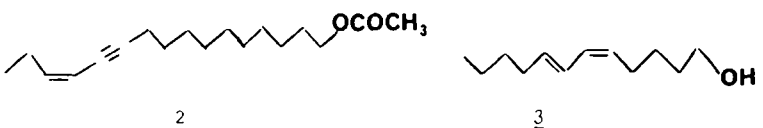
In continuation of our studies on the synthesis of pure polyunsaturated insect sex pheromones[2-4] we now report the application of this method to the synthesis of (*Z*)-13-hexadecen-11-yn-1-yl acetate (**2**), the sex pheromone of the processionary moth, *Thaumetopoea pityocampa*,[5] the most important defoliator pest of pine trees in the Mediterranean countries, and of (5*Z*,7*E*)-5,7-dodecadien-1-ol (**3**), a sex pheromone component of the forest tent caterpillar, *Malacosoma disstria*,[6] a defoliator of the trembling aspen and other trees in North America.

RESULTS AND DISCUSSION

Compound **2** was prepared according to the sequence depicted in Scheme 1, in which (*Z*)-1-iodo-1-butene (**6**) and 11-dodecyn-1-ol (**7**) were used as key compounds. 1-Butyne (**4**) was converted into 1-lithium-1-butyne which reacted with a molar excess of I_2 to give 1-iodo-1-butyne (**5**) in 82% yield.

Treatment of **5** with dicyclohexylborane, followed by protonolysis afforded stereochemically pure **6** in 38% overall yield.

Pure 11-dodecyn-1-ol (**7**), which was prepared by reaction of 10-bromo-1-(2-tetrahydropyranloxy)decane with lithium acetylide-ethylenediamine complex followed by acid hydrolysis,[8] was reacted with a molar excess of **6**. The reaction was carried out at room temperature under phase transfer conditions employing benzyltriethylammonium chloride as phase transfer agent, a large excess of 2.5N NaOH as base, and a mixture of tetrakis(triphenylphosphine)palladium and cuprous iodide as catalyst. The molar ration Cu/Pd was 4.6. The mixture which did not contain unreacted **7**, after treatment with ammonium chloride solution was extracted with hexane and filtered. The filtrate was concentrated and purified from the catalyst by chromatography to give



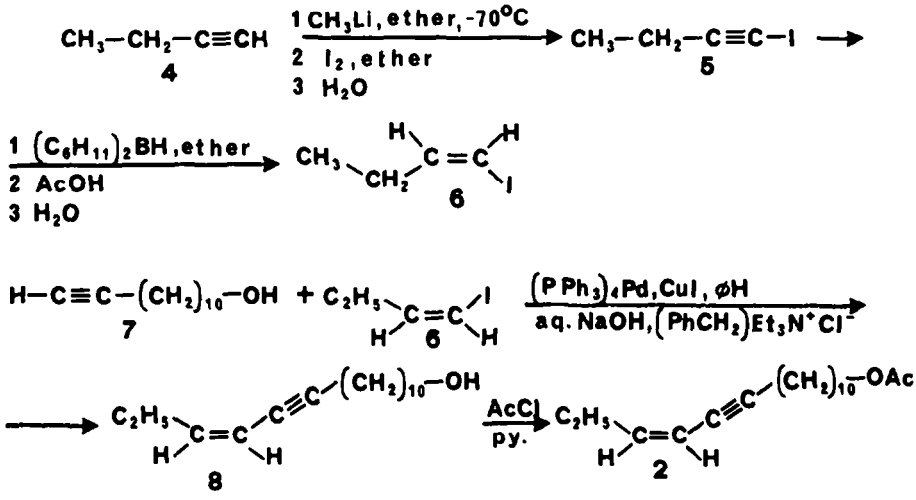
2

3

One or more stereoisomers of 5,7-dodecadien-1-ol are very probably sex pheromone components of the pine moth, *Dendrolimus spectabilis*.[7]

To our knowledge, detailed syntheses of these two important compounds have not been so far reported.

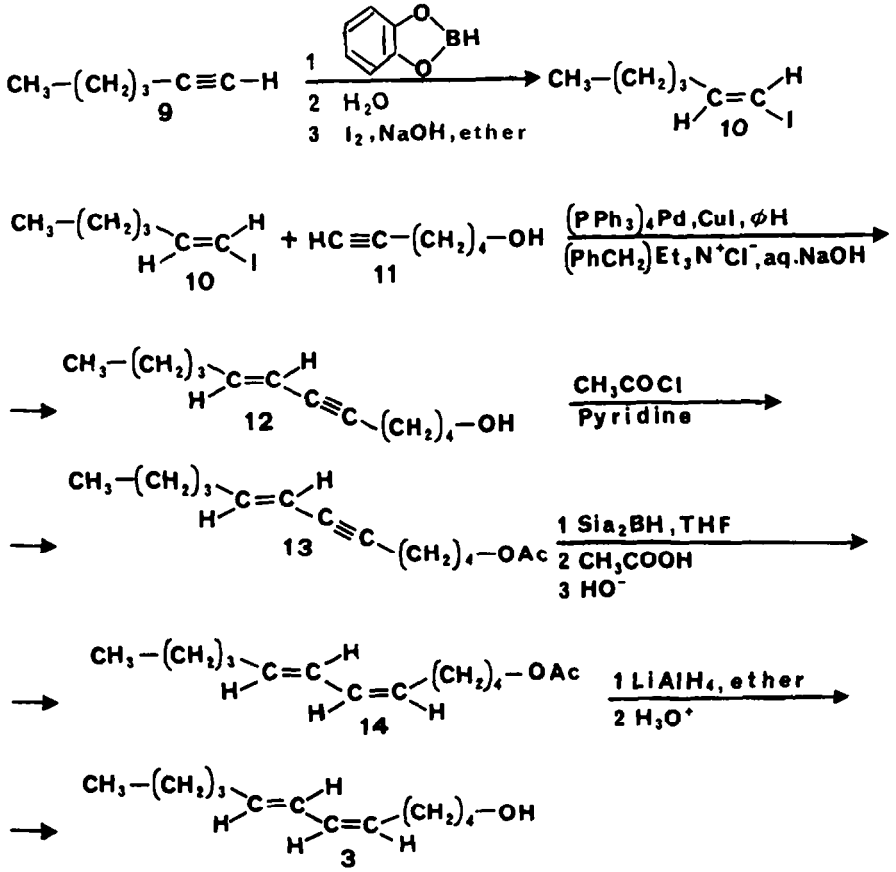
crude (*Z*)-13-hexadecen-11-yn-1-ol (**8**) in 78% yield. GLC analysis showed that **8** had chemical and stereoisomeric purity higher than 98%. The alcohol was then acetylated to give **2** having physical properties identical with those of the natural compound.[5]



Scheme 1.

The dienic sex pheromone component **3** was synthesized by coupling a 1-halo-1-alkene, i.e. (*E*)-1-iodo-1-hexene (**10**), with an ω-functionalized 1-alkyne, i.e. 5-hexyn-1-ol **11** (Scheme 2). Compound **10** was prepared as reported[1] by heating a mixture of 1-hexyne (**9**) and catecholborane,[9,10] hydrolysing the 2[(*E*)-1-hexenyl]-1,3,2-benzodioxaborole and treating the derived boronic acid with an ether solution of J_2 and aqueous sodium hydroxide.[9] GLC analysis showed that **10** had 99% stereoisomeric purity and contained *ca* 2.5% of an impurity probably 2-iodo-1-butene. 5-Hexyn-1-ol (**11**) was obtained starting from 4-chloro-1-(2-tetrahydropyranyloxy)butane by a sequence identical to that followed to prepare **7**. Then, according to the procedure employed to prepare **8**, the iodide **10** was coupled with molar defect of **11** to give (*E*)-7-dodecen-5-yn-1ol (**12**) in 70% yield.

Such a compound, with chemical and stereoisomeric



Scheme 2.

purity identical to that of **10**, was converted into the corresponding acetate **13** and subsequently stereoselectively reduced to (5*Z*,7*E*)-5,7-dodecadien-1-yl acetate (**14**) by treatment with disiamylborane in tetrahydrofurane, followed by protonolysis and and reaction with hydrogen peroxide (89% overall yield). The sex pheromone component **3** was obtained from **13** by reaction with lithium alanate followed by acid hydrolysis. GLC analysis showed that **3** had 99% chemical purity and 97.2% isomeric purity.

It is interesting to note that Vu *et al.*[7] have already reported, without experimental details, a synthetic scheme for the preparation of **3** similar in part to that described. The authors coupled (*E*)-1-iodo-1-hexene with the tetrahydropyranylether of **11** in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide to obtain (*E*)-1-(2-tetrahydropyranyloxy)-7-dodecen-5-yne. Removal of the tetrahydropyranyl group and hydrogenation over Pd–$BaCO_3$ gave **3**.[7] Although these authors do not report either the reaction yields, or the characterization of the products, some remarks may be made on their synthetic scheme. In our hands the coupling reaction of 1-alkynes with 1-halo-1-alkenes in the presence of $(PPh_3)PdCl_2$ and Cu J gave rise to lower yields than those of the reaction catalyzed $(PPh_3)_4Pd$ and CuJ, under phase transfer conditions.[1] Moreover, in our experience the reduction of internal (*E*)- or (*Z*)-1,3-enynes with hydrogen in the presence of Pd catalysts affords very complex mixtures from which it is very difficult to separate the desired pure (*E*,*Z*)- or (*Z*,*Z*)-conjugated dienes. The only method so far developed to reduce stereoselectively and in high yield the triple bond of conjugated internal enynes, is that based on the use of disiamylborane.

In conclusion, the above syntheses represent rather convenient methods to prepare relatively large amounts of the sex pheromone of *T. pityocampa* and of a sex pheromone component of *M. disstria* in high chemical and stereoisomeric purity. In our opinion the only drawback to the extension of these syntheses to a large scale preparation is due to the fact that the (*Z*)- or (*E*)-1-halo-1-alkenes used as starting materials are expensive. We are currently investigating synthetic methods based on the use of stereoselective transition metal-catalyzed reactions which do not present this limitation.

EXPERIMENTAL

All b.p. are uncorrected. IR refer to films and were determined on a Perkin–Elmer 225 spectrometer. Mass spectra were recorded on a Varian Mat–CH 7 spectrometer. ^{1}H NMR spectra were recorded at 60 MHz on a Varian T60 spectrometer using TMS as internal standard. GLC analyses were performed on a DANI 3900 glass capillary column dedicated gas-chromatograph using a Carbowax 20 M glass capillary column (30 m × 0.3 mn i.d.) and a FID detector.

All Pd catalyzed reactions were carried out under N_2 and the deareated liquids were transferred with hypodermic syringes or double-ended needles.

(*Z*)-1-*Iodo*-1-*butene* (6). A 2 M ether soln of MeLi(0.4 mol) was slowly added to a stirred ether soln (250 ml) of **4** (22.2 g, 0.395 mol) cooled at −70°. The mixture was stirred for 1 h at −50° and then cooled at −70°. An ether soln (700 ml) of I_2 (120.1 g, 0.47 mol) was slowly added to the ether soln of 1-lithium-1-butyne. The mixture was stirred for 0.5 h at −70° and after the temp was allowed to rise to room temp. It was poured into ice-water and extracted with ether. The ether extracts were washed with $Na_2S_2O_3$ aq, and water, dried and concentrated at 100 torr. The residue was fractionally distilled to give **5** (58.3 g, 82% yield): b.p. 67–70°/80 torr. Such iodide was slowly added to an ether soln of dicyclehexylborane cooled at 0° prepared starting from borane–dimethylsulfide complex (30.85 g, 0.406 mol) in ether (360 ml) and cyclohexene (66 g, 0.812 mol). The mixture was stirred at 0° for 1 h and at 20° for 2.5 h. A OH (202 ml) was added and the resulting mixture was stirred for 12 h at room temp. It was then poured into a large excess of water and extracted repeatedly with ether. The ether extracts were neutralized and concentrated at room temp and at 160 torr. The residue was then distilled at 15 torr collecting the low-boiling product into a trap cooled at −70°. Fractional distillation of this product gave **6** (27.5 g; 38% overall yield): b.p. 62%/106 torr. ^{1}H NMR (CCl_4): δ 6.42–6.01 (m, 2H), 2.45–1.94 (m, 2H); 1.05 ppm (*t*, 3H) GLC analysis showed that **6** was chemically and stereoisomerically pure.

11-*Dodecyn*-1-*ol* (**7**) *and* 5-*hexyn*-1-*ol* (**11**). 11-Dodecyn-1-ol (**7**) was prepared by removal of the tetrahydropyranyl group from 12-(2-tetrahydropyranyloxy)-1-dodecyne which was obtained by reaction of 10-bromo-1-(2-tetrahydropyranyloxy)decane with lithium acetylide-ethylenediammine complex in DMSO.[8] Compound **7** had b.p. 92°/0.09 torr; n_D^{25} 1.4568; ν_{max} 3340, 3310, 2920, 2850, 2115, 1465, 1430, 1380, 1320, 715 cm^{-1}. ^{1}H NMR (CCl_4): δ3.7–3.3 (t, 2H), 3.05 (s, 1H), 2.3–2.0 (br m, 2H), 1.9–1.7 (m, 1H), 1.7–1.1 (br, 16H) (Calc. for $C_{12}H_{22}O$: C, 79.06; H, 12.12. Found: C, 78.80; H, 12.38).

5-Hexyn-1-ol (**11**) was prepared in a similar way (70% yield) starting from 4-chloro-1-(2-tetrahydropyranyloxy)butane. Compound **11** had b.p. 84°/17 torr; n_D^{25} 1.4483 (lit[11] b.p. 72–75°/10 torr). GLC analysis showed that **11** was chemically pure.

(Z)-13-*Hexadecen*-11-*yn*-1-*yl acetate* (**2**). A deareated mixture of **6** (17 g, 93 mmol) and **7** (10.3 g, 57 mmol) was rapidly added under N_2 to a mixture of benzyltrithylammonium chloride (0.7 g, 3.27 mmol) tetrakis(triphenylphosphine)palladium (2.6 g, 2.25 mmol) and cuprous iodide (2 g, 10.5 mmol) in deareated benzene (35 ml). A deareated 10% NaOHa (270 ml) was then added and the mixture was stirred mechanically at room temp for 12 h. The mixture was then diluted with water, treated with an excess of sat NH_4Claq and extracted repeatedly with hexane. The hexane extracts were filtered, washed with sat NH_4Cl aq and with water until neutrality, stirred with animal carbon and filtered. After drying and concentration the organic residue was chromatographed over silica gel (120 g, Kieselgel H-60) using benzene as eluent. The eluate was concentrated to give crude (*Z*)-**8** (10.5 g, 78% yield). GLC analysis showed that **8** had chemical and stereoisomeric purity higher than 98%.

The alcohol was then acetylated according to the lit[2] to give **2** (98% *yield*): *b.p.* 132–133°/0.05 torr; n_D^{25} 1.4688; ν_{max} 3020, 2960, 2920, 2850, 2210, 1740, 1625, 1460, 1430, 1385, 1360, 1325, 1300, 1235, 1035, 880, 790, 730 and 625 cm^{-1}. ^{1}H NMR (CCl_4): δ5.82 (m, 1H), 5.42 (d, 1H), 4.05 (t, 2H), 2.4–2.05 (br m, 4H), 2.05 (s, 3H), 1.9–1.2 (br m, 16 H), 1.03 (t, 3H). Mass spectrum *m/e* 278 (M^+, 4.7%), 94 (100%). Calc. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.61; H, 11.06. CLC analysis (column at 185°; H_2, 0.4 Kg/cm^2; temp. of detector, 300°) showed that **2** had 98% chemical and stereoisomeric purity.

(E)-1-*Iodo*-1-*hexene* (**10**). (*E*) **10** was prepared in 53.5% yield starting from **9** according to the lit.[1] Compound **10** had b.p. 70°/18 torr; n_D^{25} 1.5055 Lit[1] b.p. 66°/16 torr; n_D^{25} 1.5056). GLC analysis showed that **10** had 99% stereoisomeric purity and contained *ca* 2.5% of an impurity probably 2-iodo-butene.

(E)-7-*Dodecen*-5-*yn*-1-*ol* (**12**). According to the preparation of **2** a mixture of **10** (24.5 g, 0.117 mol) and **11** (16 g, 0.163 mol) was added to a mixture of benzyltriethylammonium chloride (1.13 g, 5.3 mmol), $(PPh_3)_4Pd$(5.3 g, 4–6) and CuJ (2.74 g, 14.4 mmol) in benzene (40 ml). A 10% NaOHaq (350 ml) was added and the mixture, after stirring for 12 h at room temp., was worked up as described. Fractional distillation of the product after chromatography on silica gel, afforded **12** (14.7 g 70% yield): b.p. 97–98%/0.09 torr; n_D^{25} 1.4886; ν_{max} 3330, 3010, 2950, 2920, 2865, 2855, 2205, 1450, 1430, 1325, 1160, 1055, 1025, 950, 925 and 725 cm^{-1}, ^{1}H NMR (CCl_4): δ 6.33–5.17 (m, 2H), 3.63 (br, 2H), 3.1 (br s, 1H) 2.55–1.87 (m, 4H), 0.93 ppm (t, 3H). Mass spectrum: *m/e* 180 (M^+). (Calc. for $C_{12}H_{20}O$: C, 79.38; H, 11.16. Found: C, 79.53; H, 11.46).

GLC analysis (column at 180°; N_2, 0.4 Kg/cm^2; temp of detector 280°) showed that **12**, had 99% chemical purity and *ca* 98% stereoisomeric purity.

(E)-7-*Dodecen*-5-*yn*-1-*yl acetate* (**13**). Reaction of **12** with acetyl chloride and pyridine in diethyl ether[2] afforded **13** in 97.5% yield. Compound **13** had b.p. 101°/0.1 torr; n_D^{25}1.4732; ν_{max} 3560, 3020, 2955, 2925, 2870, 2855, 2215, 1740, 1450, 1430, 1385, 1360, 1325, 1230, 1160, 1130, 1115, 1040, 950, 920, 840, and 725 cm^{-1}. ^{1}H NMR (CCl_4): δ 6.6–5.1 (m, 2H), 4.06 (t, 2H), 2.5–1.8 (m, 4H), 1.9 (s, 3H), 1.8–1.05 (m, 8H), 0.93 ppm (t, 3H). Mass spectrum: *m/e* 222 (M^+, 19.6%), 161 (M^+—$CH_3COOH_2^+$, 6.5%), 91 (100%). (Calc. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.85; H, 10.03).

(5Z,7E)-5,7-*Dodecadien*-1-*yl acetate* (**14**). A THF soln of disiamylborane (0.080 mol), which was prepared from a 10M soln of borane-methylsulfide and 2-methyl-2-butene,[4] was slowly added to a soln of **13** (11 g, 0.0495 mol) in THF (58 ml) cooled at −10°. The mixture was stirred for 5 h at 0°, then AcOH (19 ml) was added and the mixture was heated under stirring for 6 h at 60°. After evaporation of the volatile substances (25° at 15 torr, 0.5 hr) 6 N NaOH (110 mml) was added followed by addition of 36% H_2O_2 (added dropwise, 23.6 ml), maintaining the temp below 40°. It was stirred for 40 min at 40° and cooled.

Water was added and the aqueous layer was saturated with NaCl. The organic layer was separated and the aq layer was extracted with ether. The combined extracts were washed with sat NaClaq, dried and concentrated. The residue was fractionally distilled to give **14** (10.2 g, 91.9% yield): b.p. 90.90.5°/0.09 torr; n_D^{25}1.4707; ν 3015, 3000, 2950, 2925, 2870, 2855, 1740, 1650, 1610, 1465, 1455, 1430, 1383, 1363, 1235, 1035, 978, 945, 830 and 725 cm^{-1}. ^{1}H NMR (CCl_4): δ6.67–5.1 (m, 4 H), 4.15 (t, 2 H), 2.5–1.9 (m, 4H), 2.04 (s, 3H), 1.9–1.1 (m, 8H), 1.0 ppm (t, 3H). Mass spectrum: *m/e* 224 (M^+, 20.6%), 164 (M^+—CH_3COOH, 14.7%), 79 (100%). (Calc. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.16; H, 11.02). GLC analysis (column at 153°; N_2, 0.3 kg/cm^2; temp. of detector, 280°) showed that **14** had 99% chemical purity and 97.5% isomeric purity.

(5Z,7E)-5,7-*Dodecadien*-1-*ol* (**3**). An ether soln (40 ml) of **14** (9.1 g, 0.040 mol) was slowly added to a suspension of LAH (1.8 g, 0.047 mol) in ether (50 ml) cooled at 0°. The mixture was stirred for 12 h at room temp, then cooled at 0°, hydrolyzed with dil HCl, and extracted repeatedly with ether. The combined ether extracts were washed with water, dried and concentrated. Fractional distillation afforded **3** (6.9 g, 95% yield): b.p. 90–91°/0.05 torr; n_D^{25} 1.4865; ν_{max} 3320, 3020, 2960, 2930, 2875, 2860, 1650, 1455, 1430, 1410, 1380, 1055, 1030, 980, 945, 830 and 725^{-1}. ^{1}H NMR (CCl_4): δ6.78–5.22 (m, 4 H), 3.77 (t, 2H), 3.05 (s, 1 H), 2.65–2.02 (br m, 4 H), 2.02–1.32 (br, 8 H), 1.12 ppm (t, 3 H). Mass spectrum: *m/e* 182 (M^+, 19%); 164 (M^+—H_2O, 9%), 67 (100%). (Calc. for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.10; H, 12.36).

GLC analysis (column at 165°; N_2, 0.3 Kg/cm^2; temp of detector, 280°) showed that **3** had 99% chemical purity and 97.2% isomeric purity.

Note added in proof. Two different syntheses of compound **2** have been recently reported [G. Cardillo, A. Cugola, M. Orena and S. Sandri, *Gazz. Chim. Ital.* **112**, 231 (1982); D. Michelot, A. Guerrero and V. Ratovelomanana, *J. Chem. Res.* (S), 93 (1982].

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