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SYNTHESIS OF 12-ACETOXY-1, 3-DODECADIENE, AN INSECT SEX PHEROMONE OF THE RED BOLLWORM MOTH, FROM A BUTADIENE TELOMER

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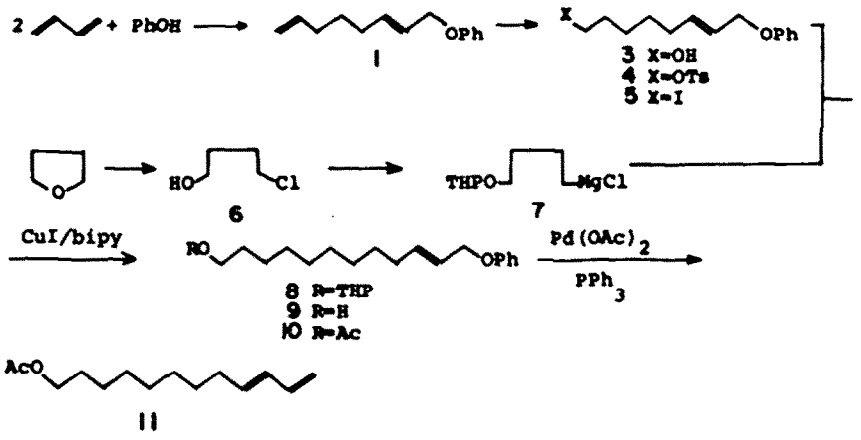
Abstract—8-Phenoxy-1, 6-octadiene (1) formed by the Pd-catalyzed telomerization of butadiene with phenol was converted to 8-phenoxy-6-octen-1-ol (3). The alcohol 3 was converted to 8-iodo-1-phenoxy-2-octene (5). The Grignard reagent 7 prepared from 4-chloro 1-butyl tetrahydropranyl ether was coupled with the iodide 5 by the catalysis of CuI and bipyridyl to give 12-phenoxy-10-dodecen-1-ol (9), which was converted to 12-acetoxy-1-phenoxy-2-dodecene (10). Finally, 12-acetoxy-1, 3-dodecadiene (11) was obtained by the palladium catalyzed elimination of phenol from phenoxyacetoxy-dodecene (10).

In a previous paper, we reported a general synthetic method for a terminal conjugated diene system by the palladium catalyzed elimination reaction of acetic acid from allylic acetates and phenol from allylic phenyl ethers.[1] We now wish to report an application of this method to a simple synthesis of an insect sex pheromone of the red bollworm moth, *Diparopsis castanea*, a major pest of cotton in Africa. The most potent of the sex pheromones produced by the virgin female moth was shown by Nesbitt *et al.* to be 12-acetoxy-1, 3-dodecadiene (11).[2] The above method of the diene synthesis is very suitable for the synthesis of this pheromone having a terminal conjugated diene system. In this synthesis, a butadiene telomer obtained by the Pd- catalyzed telomerization of butadiene with phenol[3] was used as a starting material. The telomer, namely 8-phenoxy-1, 6-octadiene (1) has necessary functionality for the synthesis of the pheromone. Pd compounds are now regarded as useful reagents in organic synthesis, especially as catalysts. In our continuous effort to apply the Pd catalysis to organic synthesis, we have reported simple synthetic methods of a number of natural products utilizing Pd catalysts in key steps.[4] In this pheromone synthesis, a Pd catalyst plays an important role in key steps.

Four synthetic methods for this pheromone have been reported. Nesbitt[5] and Babler[6] utilized the Wittig reaction for the preparation of the diene system. Coupling reaction of an allylic halide with a Grignard reagent was used in the synthesis by Mori.[7] Yamamoto *et al.* reported briefly the synthesis applying their method of 1,3-diene synthesis from allylic alcohols *via* oxirane and enediol.[8] Our synthetic approach is quite different and the method is based on four-carbon elongation of the butadiene telomer and generation of the diene system by the Pd catalyzed elimination of phenol from the allylic phenyl ether moiety. The synthesis was carried out by the following sequence of reactions.

The telomerization of butadiene with phenol catalyzed by palladium acetate and triphenylphosphine afforded 8-phenoxy-1,6-octadiene (1) as a major product, accompanied by 3-phenoxy-1, 7-octadiene. The former was isolated by fractional distillation in 78% yield. Selective hydroboration of the terminal double bond without attacking the internal double bond of 1 was carried out by the use of 9-borabicyclo[3,3,1]nonane to give a primary alcohol 3 after oxidation with hydrogen peroxide in 80% yield. The alcohol 3 was converted to tosylate 4 in 84% yield. Then the tosylate was treated with sodium iodide in boiling acetone to give iodide 5 in 95% yield. The four-carbon unit necessary for the chain elongation was derived from tetrahydrofuran, which was cleaved with hydrogen chloride to give 4-chloro-1-butanol (6). The alcohol 6 was protected by tetrahydropyranyl ether formation, and the Grignard reagent 7 was prepared. We have reported that the coupling of alkyl halides with Grignard reagents can be carried out with satisfactory yields by the use of cuprous iodide coordinated by 2,2'-bipyridyl as a catalyst system,[9] and this method was successfully applied again in the present synthesis. The coupling of 5 with 7 was carried out by dropwise addition of the Grignard reagent 7 in THF at 0° to a mixture of the iodide 5, cuprous iodide (10 mol%) and bipyridyl (10 mol%). The coupled product was purified by column chromatography to give the diether 8 in 80% yield. The tetrahydropyranyl group was removed with dilute hydrochloric acid to give crystalline alcohol 9, which was converted to acetate 10 by the treatment with acetic anhydride and pyridine. The final step of the synthesis is the diene generation which was achieved by slow distillation of the acetate 10 under reduced pressure (1 Torr) at 160° (bath temp) in the presence of catalytic amounts of palladium acetate (1 mol%) and triphenylphosphine (10 mol%), and the distilled pure pheromone 11 was collected as a colorless oil in 71% yield.

The natural pheromone has been reported to consist of 75–85% *trans*- and 25–15% *cis*-isomer,[5] while the pheromone 11 synthesized here was indicated to comprise equal amounts of *trans*- and *cis*-isomers by an



analytical method involving reduction of the terminal double bond with diimide and glc determination of the 12-acetoxy-2-dodecene isomers.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were recorded as neat films on a JASCO IRA-2 spectrometer. NMR spectra were recorded in CCl_4 on a HITACHI R-24 (60 MHz) with TMS as an internal standard.

8-Phenoxy-1, 6-octadiene (1). A mixture of phenol (9.4 g, 0.1 mol), $PdCl_2(PPh_3)_2$ (350 mg, 0.5 mmol) and sodium phenoxide (300 mg, 2.58 mmol) in benzene (10 ml) was placed in a 100 ml autoclave. Butadiene (33 ml, 0.4 mol) was introduced into the autoclave. The reaction was carried out at 60° for 17 hr. Ether (30 ml) was added. Then triphenylphosphine was added and the soln was washed with 6N HCl to precipitate the Pd catalyst. After the ppt was filtered off, the filtrate was dried over $MgSO_4$ and evaporated. The crude oil was distilled to give a mixture of 1 and 3-phenoxy-1, 7-octadiene (7:1; 18.0 g, 89%). The fractional distillation of the mixture gave pure 1 (104°/4 Torr): ^{1}H NMR (CCl_4) δ 1.55 (2H, m, $-CH_2-$), 2.05 (4H, m, $=CCH_2-$), 4.38 (2H, d, J = 4 Hz, $-OCH_2C=$), 4.72–6.20 (5H, m, olefinic), 6.63–7.40 (5H, m, aromatic); IR (neat) 1640, 1600, 1500, 1240, 990, 970 cm^{-1}.

8-Phenoxy-6-octen-1-ol (3). A 3-necked flask was charged with THF (10 ml) and 1 (8.08 g, 40 mmol) and placed in an ice bath under N_2. Then 0.5 M soln of 9-borabicyclo[3.3.1]nonane in THF (100 ml) was added slowly. The soln was stirred for 2 hr at a room temp. A mixture of 3N NaOH (30 ml) and 28% H_2O_2 (30 ml) was added dropwise at 0° and stirred for 1 hr at the room temp. The mixture was poured into a cooled aqueous sodium thiosulfate soln and the aqueous layer was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated to give a crude oil which was distilled under vacuum to give 3 (7.2 g, 81.8%; b.p. 143–5°/4 × 10^{-2} Torr): ^{1}H NMR (CCl_4) δ 1.45 (6H, broad, $-CH_2-$), 2.05 (2H, m, $-CH_2C=$), 3.05 (1H, s, –OH), 3.49 (2H, t, J = 6 Hz, $-CH_2OH$), 4.38 (2H, d, J = 4 Hz, $=CCH_2O-$), 5.68 (2H, m, –CH=CH–), 6.60–7.37 (5H, m, aromatic); IR (neat) 3360, 2948, 1601, 1590, 1500, 1245, 1080, 1058, 1035, 1013, 990, 975 cm^{-1}.

8-Phenoxy-6-octen-1-yl p-toluenesulfonate (4). A flask was charged with 3 (1.56 g, 7.09 mmol) and pyridine (20 ml). After the mixture was stirred for 10 min at −10°, *p*-toluenesulfonyl chloride (3.75 g, 21.3 mmol) was added in one portion and the mixture was stirred for 3 hr at −10 ~ 0°. The mixture was left in a refrigerator overnight, poured into ice water, and extracted with ether. The extract was washed with 3N HCl to remove pyridine, dried over $MgSO_4$, and evaporated to give a crude tosylate 4 (2.55 g). The tosylate was used in the next step without purification: ^{1}H NMR (CCl_4) δ 1.00–2.20 (8H, broad, $=CCH_2-$, $-CH_2-$), 2.45 (3H, s, *p*-methyl), 3.95 (2H, t, J = 6 Hz, $TsO-CH_2-$), 4.40 (2H, d, J = 4 Hz, $PhO-CH_2C=$), 5.65 (2H, m, –CH=CH–), 6.60–7.88 (9H, m, aromatic); IR (neat) 2940, 1600, 1590, 1500, 1360, 1245, 1195, 1180, 1100, 960, 910, 820, 760, 670, 560 cm^{-1}.

8-Iodo-1-phenoxy-2-octene (5). A mixture of crude 4 (2.55 g) and NaI (3.15 g, 21.0 mmol) in dry acetone (30 ml) was refluxed under N_2 for 2 hr. Acetone was removed by evaporation and the reddish residue was extracted with ether. The extract was washed with an aqueous sodium thiosulfate soln and brine, dried over $MgSO_4$, and evaporated to give the crude 5, which was purified by column chromatography (silica gel, n-hexane-ether) to give the pure 5 (1.87 g, 80% from 3): ^{1}H NMR (CCl_4) δ 1.00–2.40 (8H, broad, $=CCH_2-$, $-CH_2-$), 3.11 (2H, t, J = 6 Hz, $-CH_2I$), 4.40 (2H, d, J = 4 Hz, $-OCH_2C=$), 5.68 (2H, m, –CH=CH–), 6.64–7.40 (5H, m, aromatic); IR (neat) 2948, 1600, 1590, 1495, 1243, 1175, 1080, 1030, 1010, 990, 970, 755 cm^{-1}.

4-Chloro-1-butyl tetrahydropyranyl ether. 4-Chloro-1-butanol was prepared by the known method.[10] A mixture of 4-chloro-1-butanol (4.56 g, 42.1 mmol), 2,3-dihydropyran (5.69 g, 67.6 mmol) and a catalytic amount of *p*-toluenesulfonic acid in CH_2Cl_2 (20 ml) was stirred in a 50 ml flask under N_2 for 1 hr in an ice bath and for another 1 hr at room temp. The mixture was poured into a cold sat $NaHCO_3$ aq. The aqueous layer was extracted with CH_2Cl_2, and the combined CH_2Cl_2 soln was washed with brine and dried over $MgSO_4$. After removal of CH_2Cl_2, a pale yellow liquid (8.78 g) was obtained and chromatographed over silica gel. The product was distilled to afford pure 4-chloro-1-butyl tetrahydropyranyl ether (7.31 g, b.p. 92°/7 Torr, 87.3%): ^{1}H NMR (CCl_4) δ 1.3–2.2 (10H, broad, $-CH_2-$), 3.1–4.1 (6H, m, $-OCH_2-$, $-CH_2Cl$), 4.5 (1H, s, –OCHO–).

Grignard reagent 7. In a 100 ml 3-necked flask, flushed with N_2, fitted with a condenser, a rubber septum and a magnetic bar, was placed sliced Mg (1.99 g, 82.0 mmol). To the flask, 4-chloro-1-butyl tetrahydropyranyl ether (9.91 g, 51.5 mmol) in THF (30 ml) was added dropwise, and a small piece of I_2 was added as an initiator. Then THF (30 ml) was added and the mixture was stirred for 2 hr at 50°. Normality of the reagent was about 0.50 N by titration with 0.1 N HCl.

12-Phenoxy-10-dodecen-1-yl tetrahydropyranyl ether (8). To a 100 ml flask, flushed with N_2, fitted with a magnetic bar and a rubber septum, was added a mixture of CuI (283 mg, 1.5 mmol), bipyridyl (234 mg, 1.5 mmol) and THF (4 ml). To the mixture, 5 (4.91 g, 14.9 mmol) in THF (10 ml) was added and the resulting mixture was stirred in an ice bath. The Grignard reagent 7 (30 ml) was added dropwise for 30 min at 0°. The soln (purple) was stirred for 2 hr at a room temp. and quenched with a sat NH_4Cl aq. After removal of THF, the resulting mixture was extracted with ether. The ethereal soln was washed with brine and dried over $MgSO_4$. After removal of ether, the resulting crude product was chromatographed over silica gel to give 8 (4.28 g, 80%): ^{1}H NMR (CCl_4) δ 1.1–1.8 (14H, broad, $-CH_2-$), 1.8–2.3 (2H, m, $=CCH_2-$), 3.1–3.9 (4H, m, $-OCH_2-$), 4.4–4.6 (3H, m, $PhO-CH_2C=$), 5.6–5.8 (2H, m, –CH=CH–), 6.6–7.3 (5H, m, aromatic); IR (neat)1600, 1590, 1498, 1240, 1032, 990, 970 cm^{-1}.

12-Phenoxy-10-dodecen-1-ol (9). A mixture of 8 (4.28 g, 11.9 mmol) in MeOH (50 ml) and 3 N HCl (30 ml) was stirred at a room temp. overnight in a 200 ml flask. After neutralization of the mixture, MeOH was removed and the resulting mixture was extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with brine and dried over $MgSO_4$. Removal of the solvent gave crude 9

(3.28 g) in a quantitative yield. The crude alcohol 9 was chromatographed over silica gel and recrystallized to afford colorless crystals of 9: m.p. 40–41°; (Found: C, 78.41; H, 10.26. $C_{18}H_{20}O_2$ Calcd: C, 78.21; H, 10.21%); MS *m/e* 276. M⁺, 276. ^{1}H NMR (CCl_4) δ 1.30 (14H, broad, $-CH_2-$), 2.05 (2H, m, $=CCH_2-$), 2.90 (1H, broad, s, –OH), 3.52 (2H, m, $-CH_2-OH$), 4.41 (2H, d, J = 4 Hz, $=CCH_2-OPh$), 5.70 (2H, m, –CH=CH–), 6.60–7.40 (5H, m, aromatic); IR (KBr) 3300, 2850, 1600, 1585, 1240, 965, 750, 700 cm^{-1}.

1-*Phenoxy*-12-*acetoxy*-2-*dodecene* (10). A mixture of Ac_2O (4 ml) and 12-phenoxy-10-dodecen-1-ol (2.00 g, 7.25 mmol) in dry pyridine (4 ml) was stirred overnight at a room temp. The resulting mixture was poured into water and extracted with ether. The ethereal soln was washed with 1 N HCl, sat $NaHCO_3$ aq and brine, and dried over $MgSO_4$. Removal of ether gave 10 as a colorless oil (2.15 g, 93%): ^{1}H NMR (CCl_4) δ 1.2–1.8 (14H, broad, $-CH_2-$), 1.9 (3H, s, CH_3CO-), 1.9–2.2 (2H, m, $=CCH_2-$), 4.0 (2H, t, J = 6 Hz, $-CH_2OAc$), 4.4 (2H, d, J = 4 Hz, $PhO-CH_2C=$), 5.6–5.8 (2H, m, –CH=CH–), 6.7–7.4 (5H, m, aromatic); IR (neat) 1740, 1600, 1593, 1498, 1460, 1390, 1370, 1240, 1118, 1080, 1035, 1015, 990, 973 cm^{-1}.

12-*Acetoxy*-1, 3-*dodecadiene* (11). A mixture of 10 (235 mg, 0.74 mmol), $Pd(OAc)_2$ (12 mg, 0.053 mmol) and triphenylphosphine (50 mg, 0.191 mmol) was placed in a bent glass tube and distilled under reduced pressure (1 Torr) to give a colorless oil (197 mg, bath temp. 160°). The oil was mixture of the desired compound and phenol. The mixture was purified by column chromatography (silica gel) to give pure 11 (117 mg, 71%): ^{1}H NMR (CCl_4) δ 1.38 (12H, broad, $-CH_2-$), 1.98 (3H, s, $-COCH_3$), 2.12 (2H, m, $=CCH_2-$), 4.00 (2H, t, J = 6 Hz, $-CH_2OAc$), 4.80–6.75 (5H, complex m, CH_2=CH–CH=CH–); IR (neat) 2940, 1745, 1243, 1037, 1007, 900 cm^{-1}; MS *m/e* (rel intensity), 224 (M⁺, 1.4), 182 (0.9), 165 (14), 135 (9), 121 (13), 109 (6), 108 (8), 95 (17), 94 (17), 81 (40), 80 (56), 68 (44), 67 (77), 55 (48), 54 (66), 43 (100).

Determination of cis: trans *ratio of* 12-*acetoxy*-1, 3-*dodecadiene* (11). Since the ratio of *cis*- and *trans*-isomer in the diene 11 synthesized above could not be determined by its glc analysis which showed only a single peak at *R*, 7.3 min. (the relative retention time to tetradecyl acetate: 1.12) on DEGS SCOT column (0.28 mm × 20 m) at 140° with He flow rate 30 ml/min. (split ratio: 1/100), it was reduced to 12-acetoxy-3-dodecene with diimide formed from hydrazine and H_2O_2 as follows: Stock solns of hydrazine and H_2O_2 were prepared by dissolving hydrazine hydrate (3 ml) or 30% H_2O_2 (0.4 ml) in EtOH (100 ml each). Each 100 μl of these stock solns was added into the diene 11 (*ca.* 50 μg) and held at 50–60° in a water bath. Aliquots (each 3 μl) were taken out of the mixture every 30 min and immediately analyzed by glc under the same conditions as above. As reduction proceeded, the peak height of the starting diene (at *R*, 7.3 min) decreased in proportion to increment of newly appearing twin peaks (at *R*, 3.7 and 4.0 min), which were assigned to *trans*- and *cis*-12-acetoxy-3-dodecene respectively. These results indicate that 12-acetoxy-1,3-dodecadiene synthesized above is a mixture of about equal amounts of the *cis*- and *trans*-isomer.

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