Synthesis of 7,11-Dienes from Enol Ether and Grignard Reagents Under Nickel Catalysis: Sex Pheromones of *Drosophila Melanogaster*

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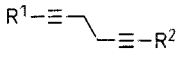
A modified Felkin reaction was used to prepare (*Z*)-4-undecen-1-ol **(5)** from hexylmagnesium bromide **(2)** and an enol ether, dihydropyran **(3)** catalyzed by low-valent nickel species, bis(diphenylphosphino)propanenickel(II) chloride **(4)**. Pyridinium chlorochromate oxidation followed by chromatography afforded (*Z*)-4-undecenal **(6)**, which was treated with hexadecyltriphenylphosphorane **(7b)** to yield (*Z,Z*)-7,11-heptacosadiene **(8b)**. Two homologs (*Z,Z*)-7,11-pentacosadiene **(8a)** and (*Z,Z*)-7,11-nonacosadiene **(8c)** were also synthesized.

The fruit fly *Drosophila melanogaster* is one of the most thoroughly studied creatures on Earth. The pioneering work of Morgan, Sturtevant, Muller, and Bridges[1] is familiar at least in derivative form to every student of high school biology, and this insect continues to play a major role in modern molecular genetics. Considering the amount of research effort devoted to this insect, it is surprising that its behavior and response to semiochemicals have not been studied in depth until recently.

Recently, the major sex pheromone of this insect has been identified as 7,11-heptacosadiene **(8b)**.[2] With minor biological activity[3,4,5] associated with 7,11-nonacosadiene **(8c)** and 7,11-pentacosadiene **(8a)**. To confirm these identifications, as well as to establish the stereochemistry of the active pheromone, we have synthesized these compounds.

Experience with Dipteran pheromones suggested that the active isomers were most probably all-*cis*; since a series of homologues is desired, a synthon containing a virtual *Z,Z*-7,11-diene system is required. The obvious candidates were 1,5-dodecadiyne **(1a)** and (*Z*)-4-undecenal **(6)**. The former, obtainable from commercially available 1,5-hexadiyne **(1b)**, could be alkylated and reduced with Lindlar's catalyst to afford the *Z,Z*-dienes; from the latter these products are available by *cis*-olefinations with the appropriate triphenylphosphoranes. We felt the latter offered the more convenient approach, as well as the opportunity to explore the application of the reaction of enol ethers and Grignard reagents under the catalytic effect of nickel species.



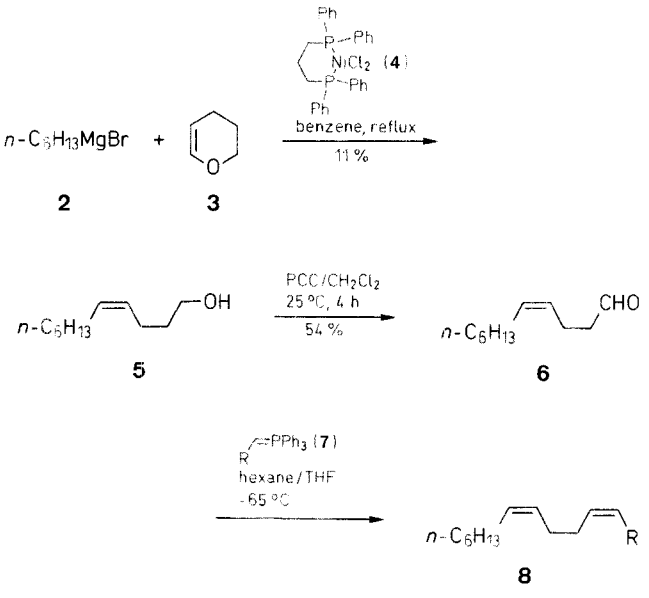
1a $R^1 = n\text{-}C_6H_{13}$, $R^2 = H$
b $R^1 = H$, $R^2 = H$

Furthermore, it has been our experience that reductions of long-chain alkenes and alkynes is often slow. We ascribe this due to irreversible adsorption of the substrate by the catalyst, since it is ameliorated by adding acetone to the solvent system. Reduction of very long-chain, trisubstituted alkenes accordingly proceeds smoothly in 20% acetone/hexane at moderate pressures. In related work, reduction of 1,20-bis(tetrahydropyranyloxy)icos-9-yne to the corresponding alkene with Lindlar's catalyst took sufficiently long (36 h) that substantial loss of stereoselectivity occurred. However, when acetone is incorporated as a cosolvent in Lindlar's catalyst reductions, the reduction cannot be stopped at the alkene stage, but proceeds smoothly to the alkane.[6] For this reason, we felt that the diyne route is undesirable.

The Felkin reaction of Grignard reagents with bis(triphenylphosphinato)nickel(II) chloride results in the replacement of the oxygen function of allylic alcohols and acetals with the alkyl group of the Grignard reagent for those Grignards, which have been termed non-reducing "Grignard reagents" (i.e., those without α-hydrogens), but gives only products corresponding to hydrogenolysis of the carbon–oxygen bond if the reagent has an α-hydrogen.[7,8] With increased understanding of the mechanism of this reaction it has been found that reduction is associated with loss of a phosphine ligand from the complex, and subsequent formation of an hydrido complex.[9,10] The ratio of alkylation/reduction is therefore greatly increased by use of catalyst containing a chelating diphosphine ligand such as bis(1,3-diphenylphosphino)propanenickel(II) chloride **(4)**.[9]

The present reaction, as described by Wenkert,[9] is one between enol (or aryl) ethers such as dihydropyran **(3)** and Grignard reagents under catalysis of low-valent nickel species. It offers an attractive route for the preparation of **6** in a stereoselective manner.

Reaction of hexylmagnesium bromide **(2)** with dihydropyran **(3)** mediated by **4**, afforded a mixture consisting of 31% 4-penten-1-ol (the product of hydrogenolysis), 17% dodecane (Wurtz product), and 40% of 4-undecen-1-ol as a mixture of *Z*- and *E*-isomers. This mixture of isomers (85% *Z* by GC) is readily resolved by column chromatography on silica gel of the undecenol fraction obtained by vacuum distillation, and the *E*-isomer identified by its IR spectrum ($\nu = 965\ cm^{-1}$). The yield of this reaction (46% undecen-1-ol **(5)**, based on the Grignard reagent) is disappointingly low, and the ratio of alkylation to hydrogenolysis product is more typical of that obtained with the non-chelated bis(triphenylphosphinato)nickel(II) chloride (1.5:1 in both cases) than that expected for the chelated phosphine complex **4** (5.7:1).[10] The amount of dodecane, derived by oxidation of the Grignard reagent, is commensurate with our previous experience with Grignard reactions, which require distillation to replace the diethyl ether solvent with benzene.



Oxidation of the (*Z*)-undecen-1-ol **(5)** with pyridinum chlorochromate (PCC) afforded the aldehyde **6** in 54% yield. Subsequent *cis*-olefination[11] with hexadecyltriphenylphosphorane **(7b)** proceeded in 99% yield to afford (*Z,Z*)-7,11-heptacosadiene **(8b)**. Compounds **8a** and **8c** were prepared in a similar fashion using tetradecyl- and octadecyltriphenylphosphorane, respectively; Kovats' indices (KI) were 2551 for **8a**, and 2963 for **8c** on DB-1. High resolution mass spectra for each homolog were also obtained. The presence of four isolated olefinic carbons is indicated by their ^{13}C-NMR spectra ($\delta = 129.161$, 129.170, 130.360, and 130.372) and their predominantly *cisoid* nature verified by the absence of significant absorption in the 900 cm^{-1} region of the IR spectra for each material.

Samples of **8b** were isomerized with nitrous acid to afford mixtures of the possible geometric isomers for comparison.[12] The resulting mixtures were resolved by argentation TLC (Redicoats, 10% silver, 0.5 mm, developed by 5% diethyl ether in hexane). Based upon the relative mobilities of the isomers in this system, they were identified as *Z,Z*- (R_f 0.15, KI 2750) *Z, E*/*E, Z*- (R_f 0.20, KI 2732), and *E,E*- (R_f 0.35, KI 2724), the mixture being 75% *Z,Z*- on capillary GC with a DB-225 column, TP 200–300 °C/6 °/min. (Under these conditions, the *Z, E*/*E, Z*- and *E,E*-isomers were poorly resolved: the above indices were obtained with samples recovered from the thin-layer plates). The majority of each synthetic material is homogeneous with the *Z,Z* isomer in both of these analytical systems, and with the natural material.[5] By capillary GC, the *Z,Z* contents of the unisomerized dienes **8a, 8b** and **8c** were found to be 95, 95, and 94%, respectively. By repeated argentation TLC, samples of these three dienes containing less than 2.5% *Z, E*/*E, Z*-isomers and no *E,E*-isomers were prepared.

As expected, pheromonal activity is found to be associated with the *Z,Z*-isomers. The heptacosadiene **8b** showed strong sex-stimulant activity, whereas **8a** and **8c** were found to be considerably less active. Details of the biological activity determination are reported elsewhere.[4]

All reagents were of commercial quality from freshly opened containers and used without further purification. Et_2O, benzene, and other reagent grade solvents were purchased from Fisher Scientific. Florisil and silica gel (60–200 mesh) was purchased from J.T. Baker Co. Argentation analytical TLC plates were purchased from Supelco. HRMS were obtained on a Kratos MS-30 instrument. Hexylbromide was purchased from Eastman Chemical Co. Catalyst **4** was purchased from Strem Chemical Co. Methyl Grignard reagent, BuLi and PCC were purchased from Aldrich Chemical Co. C-NMR spectra were obtained using a Nicolet NT-300 instrument.

(*Z*)-4-Undecen-1-ol (5):

Magnesium chips (5.6 g, 0.23 mol) are placed in a dried, Ar-purged 250 mL round-bottom flask, and freshly distilled hexyl bromide (38.5 g, 0.23 mol) in Et_2O (100 mL) is added to form hexylmagnesium bromide (0.23 mol). In a dry, Ar-purged 1 L flask is placed bis(diphenylphosphino)propanenickel(II) chloride **(4**; 5 g, 9.2 mmol) and dry benzene (150 mL). To reduce the catalyst, 2.85 M methyl Grignard reagent (7.36 mL, 2 equiv) is added, and the system refluxed for 15 min. The hexyl Grignard reagent is transferred into this dark green-brown solution by needle. Most of the Et_2O is removed by distillation, and of dry benzene (500 mL) and dihydropyran (**3**; 30 mL, 1.5 equiv) is added. Remaining Et_2O is removed by distillation until the still head temperature fell below 70 °C, and the system is refluxed overnight under Ar. Benzene is removed by distillation until only 100 mL remains, and Et_2O (400 mL) is added. The reaction is quenched by titration with sat. aq. NH_4Cl (500 mL) and the Et_2O solution filtered. The filter cake is triturated with Et_2O (500 mL), refiltered and the combined filtrates are washed with sat. aq. NH_4Cl (300 mL), brine (300 mL) and dried (Na_2SO_4). The solution is poured through a Florisil column (24 × 2 cm) topped with Celite to remove suspended catalyst, and is concentrated to give 28.4 g of oil, containing 4-undecen-1-ol (11.49 by GC). Vacuum distillation gives 4-undecen-1-ol (8.3 g, bp 78 °C/4 mbar). From this, pure (*Z*)-undecenol **(5)** is recovered by repeated column chromatography on silica gel as a clear oil; yield: 6.9 g (11%). Elution with 10% Et_2O in hexane gives first the *E*-alkenol (IR: $\nu = 965\ cm^{-1}$) followed by the *Z*-alkenol; oil (Lit.[14] oil).

IR (neat): ν = 3100–3600 (OH); 3050 cm^{-1} (C=CH).

^{1}H-NMR ($CDCl_3$): δ = 0.87 (t, 3H, J = 6.0, CH_3); 1.30 (br s, 8H, CH_2); 1.60 (pentet, 2H, CH_2CH_2OH); 1.99, 2.10 (dt, 4H, J = 6.3, CH_2CH=$CHCH_2$); 2.25 (s, 1H, OH); 3.60 (t, 2H, J = 6.5, CH_2OH); 5.38 (m, 2H, =CH).

Kovat's Index (OV-1): 1342.

MS (CI, isobutane): m/z = 170 (M^+), 171 (M^{+1}), 152 ($M^+ - H_2O$).

(*Z*)-4-Undecenal (6):
A mixture of *Z*-**5** (5 g, 29.4 mmol) and PCC[13] (9.5 g, 1.5 equiv) is stirred under N_2 in anhydrous CH_2Cl_2 for 4 h. The dark suspension is diluted 5-fold with Et_2O and poured through a Florisil column (20 g) topped with Celite. Concentration and vacuum distillation provides **6**; yield: 2.7 g (54%); bp 78°C/4 mbar (Lit.[14] bp not reported).

IR (neat): ν = 1769 cm^{-1}.

(*Z*,*Z*)-7,11-Heptacosadiene (8b); Typical Procedure:
Hexadecyltriphenylphosphonium bromide is prepared[15] from freshly distilled hexadecyl bromide and recrystallized from dioxane/CH_2Cl_2 prior to use. Hexadecyltriphenylphosphorane **(7b)** is prepared from the salt (1.83 g, 1.1 equiv) in dry THF (65 mL) and freshly titrated BuLi (1.0 equiv, 1.6 M) at −30°C. The mixture is allowed to warm to r.t. for 20 min, then cooled to −30°C and dry, freshly distilled HMPT (10 mL) is added. The mixture is cooled to −65°C and the aldehyde **6** (2.7 mmol, 0.5 g, 1 equiv) in THF (5 mL) is added dropwise over 20 min. The mixture is allowed to warm to room temperature and partitioned twice between hexane (300 mL) and water (300 mL). The organic phase is washed with brine (250 mL), dried (Na_2SO_4), and chromatographed on a silica gel column (25 × 2 cm). Elution with hexane affords **8b** as a clear oil; yield: 1.03 g (99%) (Lit.[2] oil). The spectral data (IR, NMR and MS) are comparable with those of a natural sample.

HRMS, m/z, **8b**: $C_{25}H_{48}$ requires: 348.3781 (M^+); found: 384.3756, (± 7.3 ppm) SD = ± 0.00467 (± 13.4 ppm)

IR (neat): ν = 1600 cm^{-1}.

The dienes **8a** and **8c** were prepared similarly.

8a:
HRMS, m/z: $C_{27}H_{52}$ requires: 348.3781 (m^+); found: 348.3756, (± 7.3 ppm) SD = ± 0.00467 (± 13.4 ppm)

8c:
HRMS, m/z: $C_{29}H_{56}$ requires: 404.4382 (M^+); found: 404.4376 (± 1.3 ppm) SD = ± 0.00339 (± 8.4 ppm)

Isomerization of (*Z*,*Z*)-7,11-heptacosadiene (8b) to *Z*,*E*/*E*,*Z*- and *E*,*E*-mixture:
A sample of **8b** (10 µL) in hexane (1 mL) is heated to 65°C under Ar for 30 min with 2 M $NaNO_2$ (11 µL) and 6 N HNO_3 (23 µL) with rapid stirring. The mixture is partitioned between water (1 mL) and hexane (1 mL), and the aqueous phase discarded. The organic phase is washed consecutively with 10% aq. $NaHCO_3$ (1 mL) and brine (1 mL), and dried (Na_2SO_4). Chromatography on a silica gel column (5 × 0.4 cm) in a Pasteur pipette affords the isomer mixture in the hexane eluate.

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