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An Efficient and Stereoselective Synthesis of Insect Pheromones by Way of Nickel-catalyzed Grignard Reactions[1]. Syntheses of Gossyplure and Pheromones of *Eudia pavonia* and *Drosophila melanogaster*.

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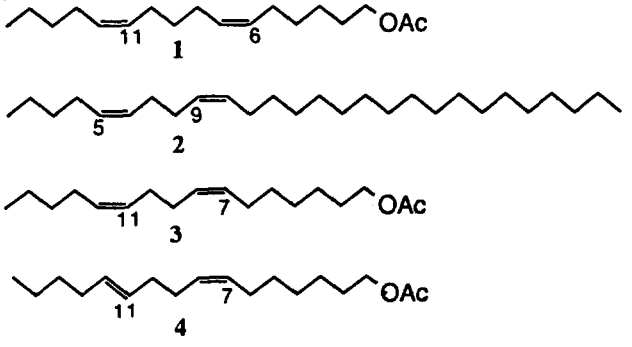
Abstract: Three pheromones, (6Z,11Z)-hexadeca-6,11-dien-1-yl acetate (from *Eudia pavonia*), (5Z,9Z)-heptacosa-5,9-diene (from *Drosophila melanogaster*) and gossyplure, have been synthesized each by two consecutive sequences of nickel-assisted Grignard reactions with cyclic enol ethers and preparation of Grignard reagents from the resultant alcohols.

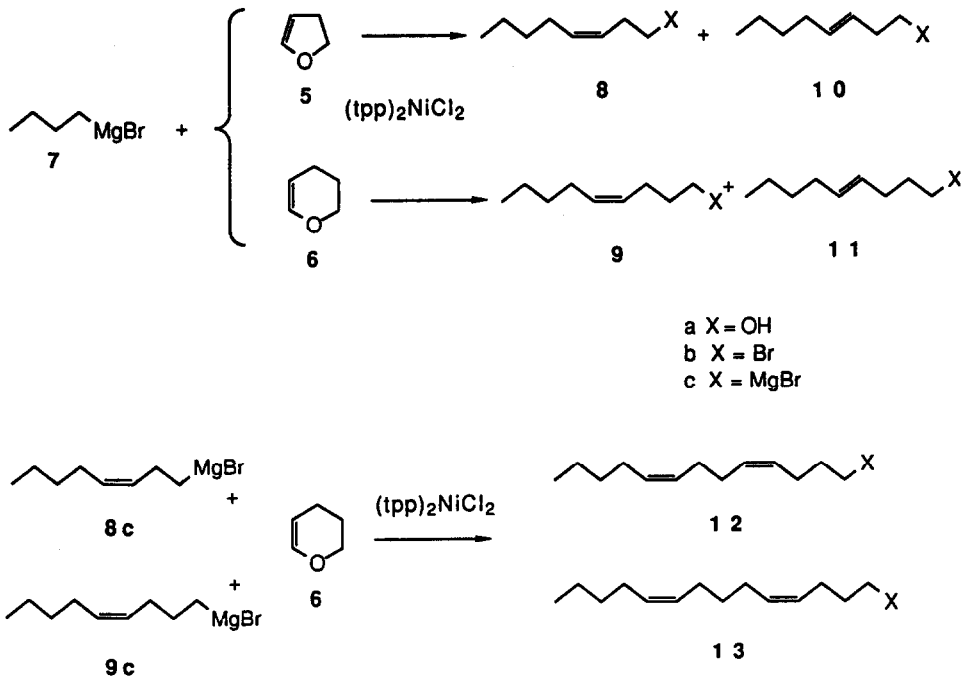
Most insect pheromones are mono- or poly-unsaturated aliphatic alcohols, acetates or aldehydes. Their biological activity depends not only on chain length and functional groups, but also on stereochemical purity and double bond position and configuration. The total synthesis of pheromones therefore requires highly stereoselective methods. The following discussion describes the application of a novel synthetic route, nickel-assisted reactions of Grignard reagents with cyclic enol ethers leading to the stereoselective formation of *Z*-olefins[3], and the application of this method to the synthesis of 1Z,5Z and 1Z,6Z pheromones. The 1Z,6Z pattern is present in (6Z,11Z)-hexadeca-6,11-dien-1-yl acetate **1**, the sex pheromone of *Eudia pavonia*[4] (Lepidoptera), while the 1Z,5Z arrangement shows up in (5Z,9Z)-heptacosa-5,9-diene **2**, a contact pheromone isolated from *Drosophila melanogaster*[5] (Drosophila).



The pheromone of *Pectinophora gossypiella* (Lepidoptera)[6], the pink bollworm, an economically important pest was chosen to demonstrate the flexibility of the approach. Male pink bollworms are attracted by a 1:1 mixture of (7*Z*,11*Z*)- (**3**) and (7*Z*,11*E*)-hexadeca-7,11-dien-1-yl (**4**) acetates. Due to its economic interest several syntheses of this pheromone blend have been carried out earlier by the use of either Wittig reactions or selective reductions of enynes for the creation of the requisite double bonds.[7]

The nickel-assisted reaction of Grignard reagents with cyclic enol ethers is an approach well suited for the stereoselective synthesis of many unsaturated compounds.[3,8] The cyclic enol ethers 2,3-dihydrofuran (**5**) and 3,4-dihydro-2*H*-pyran (**6**), used in the present approach, are cheap, commercially available compounds with an established double bond geometry, thus constituting useful starting materials for many natural product syntheses. The possible use of sequential Grignard reactions on either enol ether allowed the introduction of a general method of synthesis of dienes as shown in scheme 1. Since the products possess a functional group at a terminal carbon site, their chain length could be adjusted easily by standard methods.

Scheme 1



In order to determine the requirements for maximum selectivity, a detailed study of the coupling reactions between *n*-butylmagnesium bromide (**7**) and ethers **5** and **6** was undertaken. Within the experimental conditions described previously[3c,d] the influence of solvent, reaction temperature and type of catalyst ligand on the stereoisomeric purity of (3*Z*)-oct-3-en-1-ol (**8a**) and (4*Z*)-non-4-en-1-ol (**9a**) were investigated.

TABLE 1. Coupling Products[a] of the Nickel-catalyzed Reactions of Ethers **5** and **6** with *n*-Butylmagnesium bromide (**7**) in Benzene.

Entry	Ether	Catalyst	Temperature (°C)	Time (h)	(%) Yield	*Z/E* Ratio[b]
						8a/10a
1		dpppNiCl$_2$[c]	80	20	75	0.4
2		"	60	20	75	0.7
3	**5**	"	55	20	60	1.0
4		"	20	96	35	3.0
5		(tpp)$_2$NiCl$_2$[d]	20	96	60	9.0
6		"	-10[e]	96	30	>99
						9a/11a
7		dpppNiCl$_2$	70	20	35	3.5
8	**6**	"	20	96	70	4.0
9		(tpp)$_2$NiCl$_2$	40	20	35	49
10		"	20	96	61	>99

[a] Accompanied by reduction products as reported earlier;[1,3c-d] [b] determined by capillary GC analysis;
[c] dpppNiCl$_2$ = [1,3-bis(diphenylphosphino)propane]nickel dichloride;
[d] (tpp)$_2$NiCl$_2$ = bis(triphenylphosphino)nickel dichloride; [e] in toluene.

The use of dpppNiCl$_2$ with 3,4-dihydro-2*H*-pyran (**6**) diminishes the retention of double bond configuration previously observed for 2,3-dihydrofuran (**5**).[3c,9] Lower *Z/E* ratios were obtained, when the reaction was carried out in THF or ether instead of toluene or benzene. For this reason it was necessary to remove ethereal solvents after the formation of the Grignard reagent. Higher reaction temperatures increased the percentage of the *E* isomers : **10a** and **11a** (see Table 1). Since 2,3-dihydrofuran is more reactive, much lower reaction temperatures were required, necessitating the use of toluene (instead of benzene) as solvent.[3c,d]

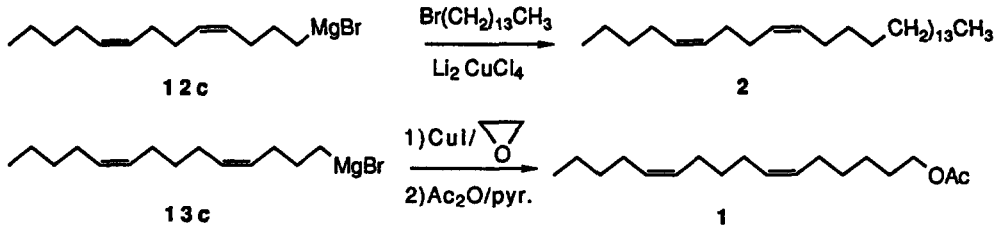
Once the optimum reaction conditions had been determined, (3*Z*)-octen-1-ol (**8a**)[7f,10] and (4*Z*)-nonen-1-ol (**9a**)[3d,4,7e,h,10a,11] could be prepared in one step in multigram quantities. Furthermore, careful choice of reaction conditions (e. g., higher temperature) allowed the preparation of well-defined *Z/E* ratios particularly adapted to the synthesis of pheromones like gossyplure (**3+4**). Before the second coupling reaction the alcohols **8a** and **9a** were transformed into their trifluoroacetates[12], which, without isolation, were converted directly into the corresponding bromides **8b**[7f,10] and **9b**.[7e,h,11b] Their Grignard derivatives **8c** and **9c** then were reacted with 3,4-dihydro-2*H*-pyran (**6**) (Table 1, entry 10, same conditions) producing (4*Z*,8*Z*)-trideca-4,8-dien-1-ol (**12a**)[7d] in 30% yield with ≥97% (*Z,Z*) stereoisomeric purity and (4*Z*,9*Z*)-tetradeca-4,9-dien-1-ol (**13a**) in 38% yield and ≥98% (*Z,Z*) stereoisomeric purity.The compounds are convenient precursors of many natural products, including the above-mentioned pheromones of *Eudia pavonia* (**1**), *Drosophila melanogaster* (**2**) and gossyplure (**3+4**). The final steps leading to compounds **1** and **2** are illustrated in Scheme 2.

(5*Z*,9*Z*)-Heptacosa-5,9-diene **2**, a contact pheromone of *Drosophila melanogaster*, was obtained in 65% yield and ≥97% (*Z,Z*) isomeric purity through coupling of the Grignard reagent **12c** with tetradecyl bromide in the presence of Li$_2$CuCl$_4$ according to Kochi's procedure.[13]

After transformation of alcohol **13a** into its bromide **13b** *via* trifluoroacetylation in a one-pot reaction, the corresponding Grignard reagent **13c** was reacted with ethylene oxide in the presence of cuprous iodide[14], furnishing alcohol **14**[15] in 60% yield (*Z,Z* ≥97%). Standard acetylation (Ac$_2$O, pyridine) of **14** led to the

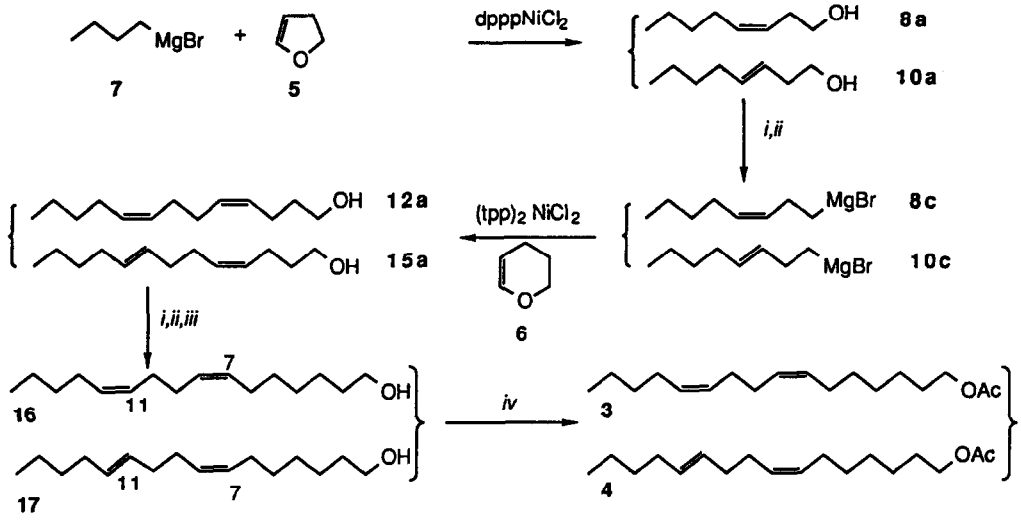
isolation of (6Z,11Z)-hexadeca-6,11-dien-1-yl acetate (**1**), the sex pheromone of *Eudia pavonia*, in 99% yield (*Z,Z* ≥ 97%).

Scheme 2



Finally, in order to demonstrate the adaptability of the present route of synthesis in the pheromone field, gossyplure, a 1:1 mixture of 7*Z*,11*Z* and 7*Z*,11*E* isomers of hexadeca-7,11-dien-1-yl acetate (**3** and **4**, respectively), was prepared. Two different procedures could be envisaged for its synthesis.

Careful control of the reaction temperature and constant GC monitoring of the *Z/E* ratios (Table 1, entry 3) in the **5-7** reaction led to 1:1 mixtures of (3*Z*)-oct-3-en-1-ol (**8a**) and (3*E*)-oct-3-en-1-ol (**10a**). The products were transformed into their bromides **8b** and **10b** with conservation of the *Z/E* ratio. The nickel-catalyzed reaction of their Grignard reagents **8c**, **10c** with 3,4-dihydro-2 *H*-pyran (**6**) (scheme 3) provided a 1:1 (± 3%) mixture of (4*Z*,8*Z*)-trideca-4,8-dien-1-ol (**12a**) and (4*Z*,8*E*)-trideca-4,8-dien-1-ol (**15a**). In order to obtain the required chain length, the mixture of alcohols was transformed into the bromides **12b** and **15b**. The Grignard reagents (**12c**, **15c**) of the halides underwent reaction with oxetane in the presence of cuprous iodide[14], furnishing a mixture of (7*Z*,11*Z*)-hexadeca-7,11-dien-1-ol (**16**) and (7*Z*,11*E*)-hexadeca-7,11-dien-1-ol (**17**). Acetylation thereof afforded gossyplure (**3**+**4**) [*Z/E* ratio = 1:1 ±5%].



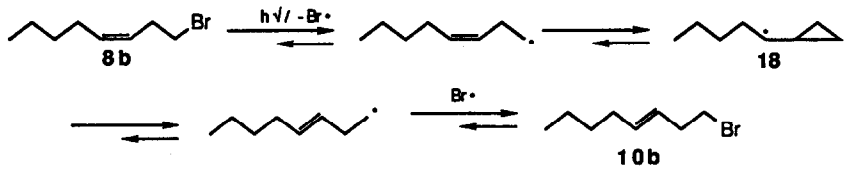
Scheme 3 : *i* :$(CF_3CO)_2O$, LiBr; *ii* : Mg/Et_2O; *iii* : oxetane/CuI; *iv* : Ac_2O/pyridine

Another pathway to gossyplure became available on observation of the *Z/E* ratio of 3-bromooctene rapidly decreasing by exposure of the substance to daylight. On irradiation of **8b** with monochromatic light (λ = 254 nm, 10 minutes) a mixture of 3-bromooctenes, whose major constituent was **10b** (*Z/E* = 0.14) was isolated. This result is reminiscent of the isomerization of unsaturated α-iodocarbonyl compounds promoted by sunlamp irradiation in the presence of hexaalkyldistannanes.[16] The photochemical equilibration can be explained by the

assumption of the formation of a bromine atom and a *cis*-homoallyl radical leading to a cyclopropylcarbinyl radical of type **18** in agreement with Beckwith's detailed analysis[17] of this type of reaction (scheme 4).

Although the same type of photochemical isomerisation is observed with (3Z)-bromonon-3-ene **9b**, a higher *Z/E* ratio (0.43) was found. The double bond isomerisations yielded a second method for obtaining a well-defined isomer mixture necessary for building compounds like gossyplure (3+4).

Scheme 4



The following scheme gave access to a precise *Z/E* ratio of 3 and 4. Pure (3Z)-oct-3-en-1-ol **8a**($Z \geq 99\%$) and a mixture of **8a** and **10a** obtained by carefully selecting the reaction conditions described in Table 1 (e.g., entries 1, 2) were prepared, followed by parallel transformation into pure **3** ($Z \geq 97\%$) and a mixture of **3** and **4** along the above described sequence. The exact 1:1 *Z/E* ratio was achieved by controlled adjustment.

Although this latter method gave the most precise *Z/E* ratio, the other scheme constitutes a good, economical synthesis complying with biological requirements.

Thus, repetition of the nickel-assisted reaction of Grignard reagents with enol ethers has led easily in four steps to acyclic dienic pheromones with high stereospecifity and good yields. Most reactions have been carried out at multigram level (up to 20 g). The synthesis of the economically important pink bollworm pheromone may constitute an advantageous alternative to previously described syntheses.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded on Bruker AM 200 SY and AM 300 spectrometers operating respectively at 200 or 300 MHz and 50.31 or 75.5 MHz in the Fourier transform mode. The carbon shifts are in parts per million (δ ppm) downfield from Me_4Si. GC product analysis was executed on a Hewlett-Packard 427 gas chromatograph with a 50 m capillary Carbowax 20M column. Infrared spectra of CCl_4 solutions or of films were recorded on a Perkin-Elmer 257 spectrophotometer. Elemental analyses were performed on a Perkin-Elmer CHN Elemental Analyzer. Mass spectra were determined on a Nermag-Sidar V 2.3 GC-MS spectrometer CI in the chemical ionization mode.

Bis(triphenylphosphino)nickel Dichloride [$(tpp)_2NiCl_2$]. The complex was prepared according to the following modification of the published procedure.[18] 26 g (99 mmol) of triphenylphosphine were dissolved by heating in 100 mL of 2-propanol and added to a solution of 12 g (50.5 mmol) of $NiCl_2 \cdot 6H_2O$ in a mixture of MeOH (20 mL) and 2-propanol (40 mL). The reaction mixture was stirred for 2 h and the temperature maintained between 60-80°C. After cooling, the green-blue powder was filtered and dried, furnishing 31.3 g (95%) of the catalyst.

[1,3-Bis(diphenylphosphino)propane]nickel Dichloride ($dpppNiCl_2$) (modified procedure[19]). 6.5 g (16 mmol) of 1,3-bis(diphenylphosphino)propane were dissolved by heating in 60 mL of 2-propanol and the resulting solution added to a solution of 4 g (16.8 mmol) of $NiCl_2 \cdot 6H_2O$ in a mixture of 2-propanol (15 mL) and methanol (5 mL). This resulted in an immediate precipitation of a red powder. The mixture was allowed to warm to 60-80°C for 15 minutes. After cooling, the red catalyst (8 g, 96%) was filtered and dried.

(3Z)-Oct-3-en-1-ol (8a). 11 mL (0.1 mol) of freshly distilled 1-bromobutane was added slowly to a stirring mixture of 2.43g (0.1 mol) of magnesium in 100 mL of anhydrous Et_2O at room temperature under argon. Titration of the Grignard reagent thus obtained indicated a yield of 75%. The ethereal Grignard solution was added dropwise to a mixture of 2.5 g (0.0038 mol, 3.8%) of $(tpp)_2NiCl_2$ in 130 mL of anhydrous toluene. After evaporation of the ether *in vacuo* (12 Torr), the reaction mixture was cooled to -10°C and 8.5 mL (0.11 mol) of 2,3-dihydrofuran was added slowly. The mixture was allowed to react for 4 days at -10°C with stirring under an argon atmosphere. The reaction was quenched by pouring the mixture into a vigorously stirring saturated aqueous NH_4Cl solution.[9] After separation of the toluene layer, extraction was achieved with ether. The combined organic layers were dried and evaporated under *vacuum*. The crude (3Z)-oct-3-en-1-ol was distilled *in vacuo* to furnish 3.1 g (30%) of the pure compound (bp 106°C, 12 Torr, stereoisomeric purity ≥ 99% as determined by GC analysis).

(4Z)-Non-4-en-1-ol (9a). 44 mL (0.409 mol) of freshly distilled 1-bromobutane was added slowly to a strirring mixture of 9.8 g (0.405 mol) of magnesium in 35 mL of anhydrous Et_2O at room temperature under argon with stirring. Titration of the Grignard reagent thus obtained indicated a yield of 70%. The ethereal Grignard solution was added dropwise to a mixture of 8 g (0.012 mol, 3%) of $(tpp)_2NiCl_2$ in 400 mL of toluene. After evaporation of the ether *in vacuo*(12 Torr), 40 mL (0.44 mol) of 3,4-dihydro-2*H*-pyran was added slowly and the mixture was allowed to react for 4 days at room temperature with stirring under an argon atmosphere. The reaction then was quenched by pouring the mixture into a vigorously stirring saturated aqueous NH_4Cl solution. After separation of the toluene layer, extraction was achieved with ether. The combined organic layers were dried and evaporated under *vacuum*. The crude (4Z)-non-4-en-1-ol was distilled under reduced pressure to furnish 24.3 g (61%) of the pure compound (bp 110°C, 12 Torr).

(3Z)-Bromooct-3-ene (8b). 27 mL (0.196 mol) of trifluoroacetic anhydride was added to a solution of 21.8 g (0.17 mol) of (3Z)-oct-3-en-1-ol (**8a**) in 80 mL of anhydrous THF maintained at 20°C. The mixture was stirred for 45 min at 0-5°C. After evaporation of trifluoroacetic anhydride and acid *in vacuo* (12 Torr), a solution of 74 g (0.85 mol) of anhydrous LiBr in a mixture of 180 mL of THF and 80 mL of anhydrous DMF was added. The reaction mixture was maintained at 80°C overnight. After evaporation *in vacuo*, the mixture was poured into water and extracted as usual. The crude reaction mixture was filtered over silica gel with petroleum ether. Distillation under vacuum (12 Torr) afforded pure (3Z)-bromooct-3-ene (**8b**) (32 g, 99%, stereoisomeric purity ≥ 99% as determined by GC analysis) : bp 90°C/ 12 Torr; IR (CCl_4) C=C 1655 (w), =CH 730(m), 640(m) cm^{-1}; ^1H NMR δ 0.8-1.0 (m, 3, Me), 1.3-1.5 (m, 4), 1.9-2.2(m, 2), 2.5-2.7 (m, 2), 3.39 (t, 2, J = 7Hz, H-1), 5.25-5.65 (m, 2, olefinic Hs); ^{13}C NMR δ 13.6 (C-8), 22.0 (C-7), 26.9 (C-5), 30.6 (C-6), 31.4 (C-2), 31.9 (C-1), 125.4 (C-4), 132.5 (C-3); mass, *m/e* 192 (M^+ ^{81}Br, 11), 190 (12, M^+ ^{79}Br, 12), 150 (29), 148 (29), 111 (8), 81 (32), 69 (100), 67 (44), 55 (96), 41 (97).

(4Z)-Bromonon-4-ene (9b). Following the procedure for the **8b** preparation (4Z)-non- -4-en-1-ol (**9a**) was converted into its bromide (99%) : bp 100°C/ 12 Torr; IR (CCl_4) C=C 1650 (w), =CH 710 (m), 695 (m) cm^{-1}; ^1H NMR δ 0.90 (m, 3 , Me), 1.25-1.40 (m, 4), 1.8-2.3 (m, 6), 3.41 (t, 2, J = 7 Hz, H-1), 5.2-5.6 (m, 2 , olefinic Hs); ^{13}C NMR δ 13.9 (C-9), 22.2 (C-8), 25.5 (C-3), 26.9 (C-6), 31.8 (C-7), 32.6 (C-2), 33.1 (C-1), 127.2 (C-4), 131.6 (C-5); mass, *m/e* 206 (M^+ ^{81}Br, 11), 204 (M^+ ^{79}Br, 12), 150 (14), 148 (15), 109 (5), 107 (5), 95 (23), 83 (68), 69 (91), 55 (100), 41 (40).

(4Z,8Z)-Trideca-4,8-dien-1-ol (12a). 20.5 g (107 mmol) of (3Z)-bromooct-3-ene (**8b**) in anhydrous ether (50 mL) was added dropwise to magnesium powder (2.7 g, 110 mmol). The mixture was stirred at 30°C for 1 h and the Grignard reagent titrated as usual. After evaporation *in vacuo* (12 Torr) anhydrous benzene (150 mL) was added. The solution was transferred *via* cannula into a solution of $(tpp)_2NiCl_2$ (4.2 g, 6.4 mmol) in anhydrous benzene (100 mL). The mixture was stirred under argon for 10 min. 8.3 g (98 mmol) of 3,4-dihydro-2*H*-pyran was added dropwise *via* a syringe. The resulting mixture was stirred at room temperature

under argon for 72 h. Extraction as usual gave a residue which was purified by chromatography on Merck silica gel (350 g, 70-230 mesh), (CH_2Cl_2 as eluant) and distillation (110°C/1 Torr) to yield (4Z,8Z)-trideca-4,8-dien-1-ol (**12a**) (4.4 g, 35%) : IR (CCl_4) OH 3320 (br, m), C=C 1655 (w) cm^{-1}; ^1H NMR δ 0.8-1.0 (m, 3, Me), 1.2-1.5 (m, 6), 1.5-1.7 (m, 2), 1.9-2.2 (m, 7), 3.65 (t, 2, *J* = 7 Hz, H-1), 5.2-5.6 (m, 4, olefinic Hs); ^{13}C NMR δ 13.6 (C-13), 22.0 (C-12), 23.4 (C-3), methylenes : 26.6, 27.0, 31.6, 32.3 (C-2), 61.7 (C-1), 128.6 (C-9 or C-8), 129.0 (C-8 or C-9), 129.8 (C-4 or C-5), 130.2 (C-5 or C-4); mass, *m/e* 196 (M^+, 1), 121 (5),96 (11), 81(100), 67 (18), 55 (59), 41 (19). Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.33; H, 12.21.

(4Z,8Z)-Bromotrideca-4,8-diene (12b). Following the procedure for the **8b** preparation **12a** was converted into its bromide **12b**: bp 110°C/1 Torr.

(5Z,9Z)-Heptacosa-5,9-diene (2) (pheromone of *Drosophila melanogaster*). 4.5 g (17.3 mmol) of (4Z,8Z)-bromotrideca-4,8-diene (**12b**) in anhydrous ether (20 mL) was added dropwise under argon to magnesium powder (0.6 g, 24.7 mmol). The mixture was stirred for 2 h under argon. After titration of the Grignard reagent (14.7 mmol, 85%), the ether was removed *in vacuo* (12 Torr). Anhydrous THF (80 mL) was added and the temperature maintained at 0°C. Tetradecyl bromide (4.3 mL, 14.4 mmol) and 1 mL of a 0.1 N solution of Li_2CuCl_4[13] in THF were added and the mixture stirred under argon for 45 min. 20 mL of anhydrous THF was added to dissolve the precipitate and the resulting solution was stirred for further 3 h at 0°C. After pouring into a cooled saturated NH_4Cl solution and ether (50 mL), the phases were separated. The aqueous phase was extracted twice with ether and the combined organic layers were dried (Na_2SO_4). The solvent was removed and the residue chromatographed on $AgNO_3$ impregnated silica (20%) (petroleum ether as eluant). The compound was distilled *in vacuo* (210°C/0.5 Torr), leading to diene **2** (3.49 g, 65%) as a colorless oil : IR (film) C=C 1650 (w), =CH 720 (w) cm^{-1}; ^1H NMR δ 0.8-1.0 (m, 6, Me), 1.1-1.4 (m, 34), 1.9-2.2 (m, 8), 5.3-5.5 (m, 4, olefinic Hs); ^{13}C NMR δ 13.9 (CH_3), 14.0 (CH_3), CH_2 : 22.3, 22.6, 26.9, 27.2, 27.3, 29.3, 29.4, 29.5, 29.6, 31.9, 129.0 (2 HC=), 130.1 (HC=), 130.2 (HC=); mass, *m/e* 376 (M^+, 18), 137 (17), 123 (24), 111 (12), 109 (11), 97 (33),96 (36), 95 (23), 83 (24), 82 (25), 81 (30), 69 (26), 67 (38), 55 (100), 43 (43), 41 (62). Anal. Calcd for $C_{27}H_{52}$: C, 86.08; H, 13.92. Found: C, 86.01; H, 13.89.

(4Z,9Z)-Tetradeca-4,9-dien-1-ol (13a). The compound was obtained as described for (4Z)-non-4-en-1-ol, starting from 30.7 g (0.15 mol) of (4Z)-bromonon-4-ene (**9b**), 3 g of $(tpp)_2NiCl_2$ and 30 mL (0.33 mol) of 3,4-dihydro-2*H*-pyran. After purification of the crude reaction mixture on silica gel using 4:1 hexane-EtOAc, distillation under vacuum (0.5 Torr) afforded two fractions : 0.23 g (1.5%) of (4Z)-non-4-en-1-ol and 8.6 g (38%) of (4Z,9Z)-tetradeca-4,9-dien-1-ol (**13a**) : bp 120°C/0.5 Torr; IR (CCl_4) OH 3630 (m), OH 3330 (br,m), C=C 1650 (w), =CH 710 (m) cm^{-1}; ^1H NMR δ 0.89 (m, 3), 1.2-1.5 (m, 7), 1.63 (m, 2, H-2), 1.9-2.2 (m, 8), 3.65 (t, 2, *J* = 7 Hz, H-1), 5.3-5.5 (m, 4, olefinic Hs); ^{13}C NMR δ 13.6 (C-14), 22.0 (C-13), 23.3 (C-3), 26.3 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 29.5 (CH_2), 31.5 (CH_2), 32.3 (C-2), 61.6 (C-1), 128.9 (C-4), 129.0 (C-9), 129.7 (C-10 or C-5), 129.8(C-5 or C-10); mass, *m/e* 210 (M^+, 1), 110(19), 95 (60), 79(100), 67 (94), 55 (68), 41 (42). Anal. Calcd for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 79.78; H, 12.48.

(4Z,9Z)-Bromotetradeca-4,9-diene (13b). Following the procedure for the **12b** preparation (4Z,9Z)-tetradeca-4,9-dien-1-ol (**13a**) was transformed into its bromide. After filtration of its petroleum ether solution through silica gel (70-230 mesh) it was distilled *in vacuo* (120°C/0.5 Torr) to provide **13b** in 99% yield (Z,Z ≥ 97% as determined by ^{13}C NMR analysis)[18]: IR (CCl_4) C=C 1650 (w), =CH 710 (m) cm^{-1}; ^1H NMR δ 0.8-1.0 (m, 3, Me), 1.2-1.5 (m, 6), 1.8-2.3 (m, 10), 3.41 (t, 2, *J* = 7 Hz, H-1), 5.2-5.6 (m, 4, olefinic Hs); ^{13}C NMR δ 13.8 (C-14), 22.2 (C-13), 25.6 (CH_2), 26.8 (CH_2), 26.9 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 32.6 (C-2), 33.0 (C-1), 127.6 (HC=), 129.2 (HC=), 130.2 (HC=), 131.3 (HC=); mass, *m/e* 274 (M^+ ^{81}Br, 1), 272 (M^+ ^{79}Br, 1), 176 (12), 174 (12), 110 (13), 95 (68), 82 (28), 81 (64), 67 (65), 55 (62), 41 (100). Anal. Calcd for $C_{14}H_{25}Br$: C, 61.53; H, 9.22. Found: C, 61.16; H, 9.40.

(6Z,11Z)-Hexadeca-6,11-dien-1-ol (14). A solution of 20.3 g (0.074 mol) of (4Z,9Z)-bromotetradeca-4,9-diene (**13b**) in 25 mL of anhydrous ether was degassed through ultrasound treatment. It then was added to 1.8 g (0.074 mol) of magnesium with stirring under argon. The Grignard derivative thus obtained was titrated (68% transformation) and added dropwise to a cooled solution (-20°C) of ethylene oxide (6.5 mL, 0.111 mol) in 8 mL of anhydrous ether in the presence of 0.95 g (0.005 mol) of CuI. The temperature then was increased slowly to room temperature and the reaction mixture was stirred under argon for 4 h. After the usual workup chromatography of the crude product (20g) on silica gel (800g, 70-230 mesh) and elution with hexane gave 2.38 g (25%) of (4Z,9Z)-tetradeca-4,9-diene. Further elution with 4:1 hexane-ethyl acetate provided crude (6Z,11Z)-hexadeca-6,11-dien-1-ol (**14**), which was purified by vacuum distillation (135°C/0.5 Torr) to furnish 8.3 g (70%) of **14** (stereoisomeric purity ≥ 97% as determined by GC analysis): IR (CCl_4) OH 3620 (m), C=C 1650 (w), =CH 710 (m) cm^{-1}; ^1H NMR δ 0.8-1.0 (m, 3, Me), 1.2-1.7 (m, 13), 1.8-2.3 (m, 8), 3.64 (t, 2, J = 7 Hz, H-1), 5.2-5.6 (m, 4, olefinic Hs); ^{13}C NMR δ 13.8 (C-16), 22.1 (C-15), 25.3 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 27.0 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 31.7 (CH_2), 32.4 (C-2), 62.1 (C-1), 129.2 (HC=), 129.4 (HC=), 129.6 (HC=), 129.8 (HC=). Anal. Calcd for $C_{16}H_{30}O$: C, 80.60; H,12.68. Found: C, 80.51; H,12.73.

(6Z,11Z)-Hexadeca-6,11-dien-1-yl Acetate (1) (the sex pheromone of *Eudia pavonia*). A mixture of 1.6 g (6.9 mmol) of (6Z,11Z)-hexadeca-6,11-dien-1-ol (**14**), 3 mL of pyridine and 4 mL (42 mmol) of acetic anhydride was stirred under argon for 4 h at room temperature. The reaction mixture was acidified with cold (O°C) 10% HCl and extracted with ether. The organic phase was washed successively with sodium bicarbonate and water and finally dried over anhydrous Na_2SO_4. The crude product obtained after evaporation of the solvent was distilled under vacuum (140°C/0.5 Torr) to furnish 1.89 g (99%) of pheromone **1** (stereoisomeric purity Z,Z ≥97% as determined by GC analysis): IR (CCl_4) C=O 1740 (s), C=C 1650 (w), C-O 1235 (s), =CH 710 (m) cm^{-1}; ^1H NMR δ 0.8-1.0 (m, 3, Me), 1.2-1.5 (m, 10), 1.5-1.7 (m, 2), 1.9-2.1 (m, 8), 2.05 (s, 3, Ac Me), 4.05 (t, 2, J = 7Hz, H-1), 5.3-5.5 (m, 4, olefinic Hs); ^{13}C NMR δ 13.2 (C-16), 20.8 (Ac Me), 22.1 (C-15), 25.4 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 26.9 (CH_2), 28.3 (CH_2), 29.1 (CH_2), 29.6 (CH_2) 31.7 (C-2), 63.3 (C-1), 129.3 (HC=), 129.5 (HC=), 129.7 (HC=), 130.0 (HC=), 169.9 (C=O). Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H,11.50. Found: C, 77.19; H,11.60.

Gossyplure (3+4). Synthetic pathway I (*via* the preparation of a 1:1 **8a-10a** alcohol mixture). 11 mL (0.1 mol) of 1-bromobutane in 33 mL of anhydrous ether was added dropwise to 2.43 g (0.1 mol) of magnesium providing 0.075 mol of a Grignard reagent, which was transferred immediately into a solution of 2.1 g (3.8 mmol) of $dpppNiCl_2$ in 130 mL of dry benzene. After stirring for 10 min the solution was evaporated under vacuum (12 Torr) and the residue was heated to 55°C. Then 8.5 mL (0.11 mol) of 2,3-dihydrofuran were introduced dropwise and the reaction was allowed to proceed under argon at 55°C for 20 h. The usual workup gave 5.75 g (60%) of a 1:1 mixture of (3Z)-oct-3-en-1-ol (**8a**) and (3E)-oct-3-en-1-ol (**10a**) after vacuum distillation (106°C/12 Torr). A standard deviation of ± 2% was determined by GC analysis over several experiments.

1:1 Mixture of (3Z)-Bromooct-3-ene (8b) and (3E)-Bromooct-3-ene (10b). Following the procedure for the **8b** preparation the 1:1 mixture of (3Z)-oct-3-en-1-ol (**8a**) and (3E)-oct-3-en-1-ol (**10a**) was converted into a 1:1 mixture of **8b/10b**.

1:1 Mixture of (4Z,8Z)-Trideca-4,8-dien-1-ol (12a) and (4Z,8E)-Tetradeca-4,8-dien-1-ol (15a). Following the procedure for the preparation of **12a** the 1:1 mixture of bromides **8b** and **10b** was converted into a 1:1 **12a-15a** mixture.

1:1 Mixture of (4Z,8Z)-Bromotrideca-4,8-diene (12b) and (4Z,8*E*)-Bromotrideca-4,8-diene (15b). Following the procedure for the **12b** preparation the 1:1 mixture of alcohols **12a** and **15a** was converted into bromides.

1:1 Mixture of (7Z,11Z)-Hexadeca-7,11-dien-1-ol (16) and (7Z,11*E*)-Hexadeca-7,11-dien-1-ol (17). Prepared as **16** below from the 1:1 bromide mixture : ^{13}C NMR δ 13.9(C-16), 22.1(CH_2, *E*), 22.3(CH_2, *Z*), 25.6(CH_2), 26.9(CH_2), 27.1(CH_2), 27.4(CH_2), 29.0(CH_2), 29.6(CH_2), 31.7(CH_2), 31.9(CH_2), 32.2(CH_2), 32.7(CH_2), 62.9 (C-2), 129.1(HC=, *Z*), 129.2(HC=, *E*+*Z*), 129.6(HC=, *E*), 129.9(HC=, *E*), 130.1(HC=, *Z*), 130.3(HC=, *Z*), 130.7(HC=, *E*).

Synthetic pathway II. Interconversion of Bromides 8b and 10b. A solution of 5 g of (3Z)-bromooct-3-ene (**8b**) in 50 mL of hexane (Fluka, HPLC quality) was degassed carefully in a ultrasound cleaning bath for 30 min. Irradiation under argon in a quartz reactor at 254 nm with an immersion low-pressure mercury (HANAU TNN 15/32) lamp for 10 min afforded a mixture of **8b** and **10b** in a 0.14 ratio (determined by GC analysis).

A precise 1:1 ratio of (3Z)-bromooct-3-ene (**8b**) and (3*E*)-bromooct-3-ene (**10b**) was obtained by addition of the calculated amount of pure (3Z)-bromooct-3-ene (**8b**) (prepared from commercially available (3Z)-oct-3-en-1-ol (**8a**) [E.G.N.O.Chimie, 76430 Tancarville, France]) to the 0.14 *Z*/*E* bromide mixture of the photochemical isomerisation. The final *Z*/*E* ratio was checked by GC analysis. The mixture then was transformed into the required mixture of (7Z,11Z)-hexadeca-7,11-dien-1-ol (**16**) and (7Z,11*E*)-hexadeca-7,11-dien-1-ol (**17**) by the use of the procedure described above for the transformation of pure bromide **8b**.

(7Z,11Z)-Hexadeca-7,11-dien-1-ol (16). 0.58 g (24 mmol) of magnesium was reacted with a solution of 6.2 g (24 mmol) of (4Z,8Z)-bromotrideca-4,8-diene (**12b**) in 15 mL of anhydrous ether. The resulting Grignard reagent (75%, according to titration) was added dropwise to a cold solution (-20°C) of 4.2 g (72 mmol) of oxetane and 0.345 g (1.8 mmol) of CuI in 15 mL of ether. The reaction mixture was stirred overnight at room temperature under argon. Usual work up followed by flash chromatography (dichloromethane) and vacuum distillation (146°C/1 Torr) yielded 3.1 g (75%) of (7Z,11Z)-hexadeca-7,11-dien-1-ol (**16**) (*Z*,*Z* ≥97% according to GC measurement): IR (film) OH 3320 (m), C=C 1655 (w), =CH 720 (w) cm^{-1}; ^{1}H NMR δ 0.8-0.9 (m, 3, Me), 1.2-1.5 (m, 11), 1.5-1.7 (m, 3), 1.9-2.2 (m, 8), 3.64 (t, 2, *J* = 7 Hz, H-1), 5.3-5.5 (m, 4, olefinic Hs); ^{13}C NMR δ 13.6(C-16), 22.0(CH_2), 25.4(CH_2), 26.6(CH_2), 26.9(CH_2), 27.1(2 CH_2), 28.8(CH_2), 29.4(CH_2), 31.6(CH_2), 32.3(CH_2), 62.9 (C-2), 128.7(HC=), 128.9(HC=), 129.6(HC=), 129.9(HC=); mass, *m/e* 238(M^+,67), 149 (39), 167 (50), 123 (100), 121 (83), 111 (44), 110 (72), 109 (72), 108 (50), 107 (83). Anal. Calcd for $C_{16}H_{30}O$: C, 80.60; H,12.68. Found: C, 80.33; H,12.42.

(7Z,11Z)-Hexadeca-7,11-dien-1-yl Acetate (3) and (7Z,11*E*)-Hexadeca-7,11-dien-1-yl Acetate (4) (1:1 mixture = gossyplure). Standard acetylation of 1.82 g (7.6 mmol) of (7Z,11Z)-hexadeca-7,11-dien-1-ol (**16**) and (7Z,11*E*)-hexadeca-7,11-dien-1-ol (**17**) (1:1) with acetic anhydride and pyridine gave 2.0 g (96%) of gossyplure after the usual workup followed by distillation (148°C/1 Torr) (the *Z*/*E* ratio being confirmed by GC and ^{13}C NMR analyses[20]) : IR (film) C=O 1745 (s), C=C 1650 (w), C-O 1235 (s), =CH 720 (w) cm^{-1}; ^{1}H NMR δ 0.8-0.9 (m, 3, Me), 1.2-1.5 (m, 10), 1.5-1.7 (m, 2), 1.9-2.2 (m, 8), 2.05 (s, 3, Ac Me), 4.05 (t, 2, *J* =7 Hz, H-1), 5.3-5.5 (m, 4, olefinic Hs); ^{13}C NMR δ 13.8(C-16), 20.7(Ac Me), 21.9(CH_2), 22.1(CH_2), 25.6(CH_2), 26.7(CH_2), 26.9(CH_2), 27.1(CH_2), 27.2(CH_2), 28.3(CH_2), 28.6(CH_2), 29.3(CH_2), 31.5(CH_2), 31.7(CH_2), 32.0(CH_2), 32.5(CH_2), 64.3 (C-2), 128.8(HC=), 129.1(HC=), 129.4(HC=), 129.6(HC=), 129.8(HC=), 130.0(HC=), 130.5(HC=), 170.8 (C=O); mass, *m/e* 280 (M^+, 43), 135 (43), 121 (43), 110 (43), 109 (43), 107(14), 96 (43), 95 (57), 94 (43), 93 (71), 91 (57), 83 (43), 81(100), 80 (43), 77 (43), 67(57), 55(30), 43 (29). Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H,11.50. Found: C, 76.98; H,11.39.

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References and Notes

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