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AN EASY ROUTE TO INSECT PHEROMONES WITH A *E-Z* or *Z-E* CONJUGATED DIENE STRUCTURE

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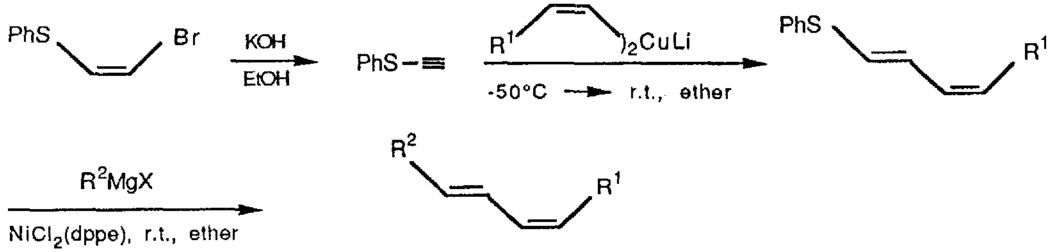
Summary: Insect pheromones having a conjugated diene system of *E-Z* or *Z-E* configuration can be prepared with high stereoselectivity, by means of addition reactions of *Z*-dialkenyl cuprates to phenylthioacetylene. The alkadienyl sulphides intermediates are then subjected to a cross-coupling reaction with Grignard reagents, in the presence of a Ni(II) complex as a catalyst, leading to the desired pheromones.

The conjugated diene system represents an important structural feature of many insect pheromones and other biologically active compounds and many methods have been developed for the stereoselective synthesis of conjugated dienes[2-9]. These methodologies frequently require the Wittig type approach[3] or the direct coupling reaction of two vinyl groups[4-7], particularly the transition metal catalyzed coupling of a stereodefined vinyl electrophile with a stereodefined alkenyl metallic compound, such as vinyl borates[4], vinyl zinc reagents prepared in situ from vinyl cuprates[5], alkenylaluminum or zirconium reagents[6], or vinyl tin reagents[7]. Furthermore, conjugated dienes can be obtained from 1,3-enynes, by the selective reduction of the acetylenic unit[8].

We recently described a general approach to mono-olefinic insect sex pheromones of *Z* - or *E*-configuration using sequential cross-coupling reactions[10] of Grignard reagents with (*Z*)- or (*E*)-1-bromo-2-phenylthioethene under Ni(II) or Pd(II) catalysis. Now we wish to report that using a variation of our method, conjugated dienes of *E-Z* or *Z-E* configuration can be prepared with high stereoselectivity. The novel procedure involves the addition reactions of *Z*-dialkenyl cuprates, generated according to the Normant method[5], to phenylthioacetylene, which in turn can be easily prepared from (*Z*)-1-bromo-2-phenylthioethene[10e,11,12]. The stereodefined alkadienyl sulphide intermediate is then subjected to the cross-coupling reaction with Grignard reagent, in the presence of a Ni(II) complex as a catalyst, leading to the desired diene (**Scheme 1**).

Scheme 1



dppe=$Ph_2PCH_2CH_2PPh_2$

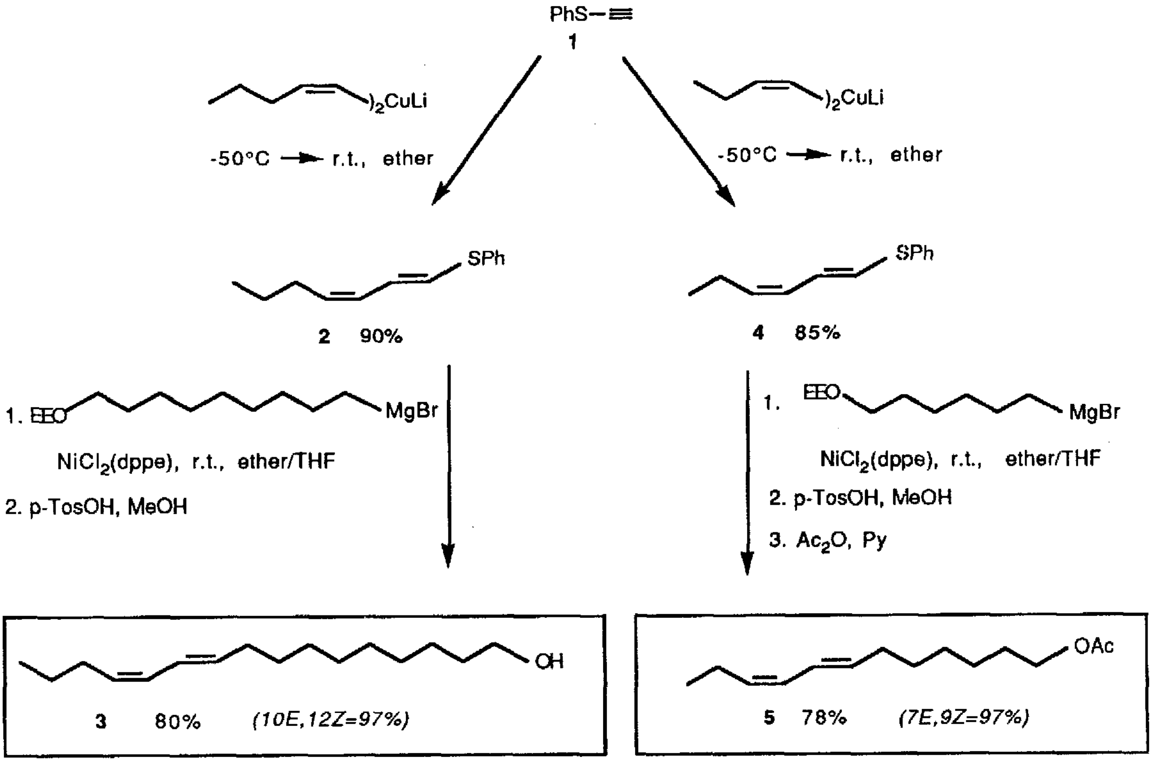
The procedure has been applied to the synthesis of insect sex pheromones of *E-Z* configuration, (**Scheme 2**), such as (10*E*,12*Z*)-10,12-hexadecadien-1-ol (**3**), bombykol, the pheromone of *Bombyx mori*[13], the silkworm moth, and (7*E*,9*Z*)-7,9-dodecadien-1-yl acetate (**5**), the pheromone of *Lobesia botrana*[14], the European grape vine moth. In an equally straightforward manner we have prepared compounds having a *Z-E* configuration, (**Scheme 3**), such as (9*Z*,11*E*)-9,11-tetradecadien-1-yl acetate (**7**), the pheromone of *Spodoptera littoralis*[15], the Egyptian cotton leafworm, and (5*Z*,7*E*)-5,7-dodecadien-1-ol (**9**), the pheromone of *Malacosoma disstria*[16], the forest tent caterpillar.

In order to prepare pheromones having the conjugated diene system with a *E-Z* configuration, the phenylthioacetylene **1** was allowed to react with a *Z*-dialkenyl cuprate[5] leading to the dienyl sulphides **2** or **4** (97% stereoisomeric purities as evidenced by GLC analysis, using a fused silica capillary column, SE 30, 30 m). The coupling reaction with functionalized Grignard reagents afforded the pheromone **3**, after removal of the protecting group, or the pheromone **5**, after the deprotection and the acetylation steps. Due to a complete retention of configuration, the stereoisomeric purities of the final products were equals to those of the intermediate dienyl sulphides.

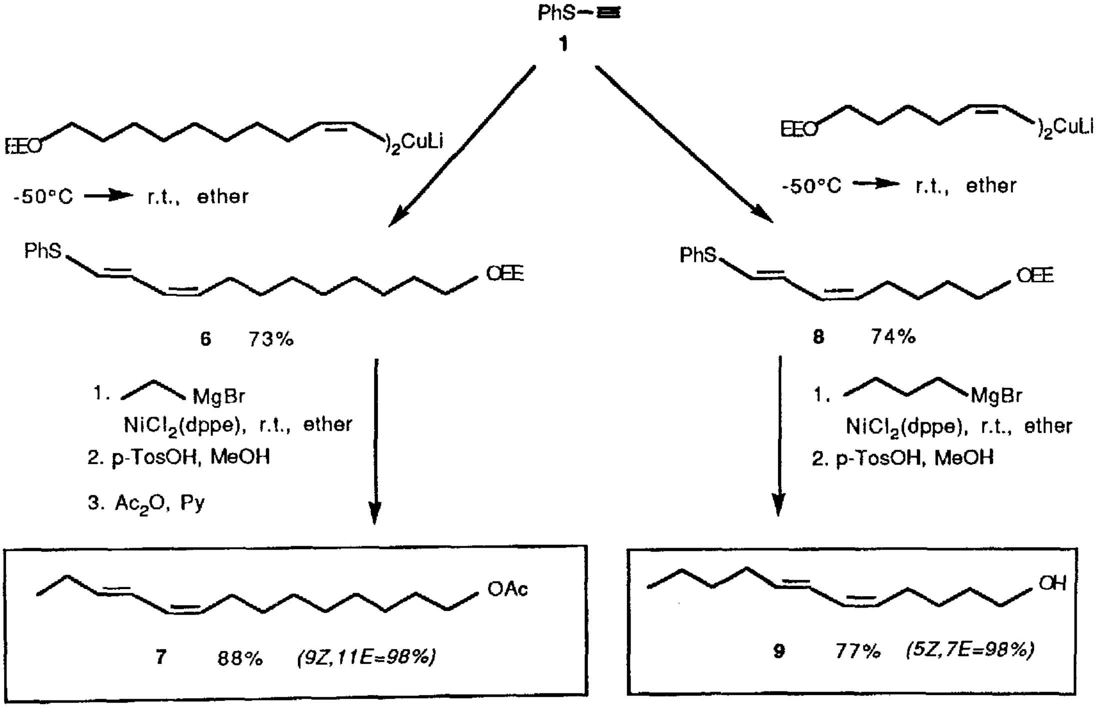
To obtain pheromones with a *Z-E* configuration it was sufficient to add a functionalized *Z*-dialkenyl cuprate[5] to phenylthioacetylene **1**. The resulting stereodefined alkadienyl sulphide (**6** or **8**) was then subjected to a coupling reaction with the appropriate Grignard reagent to give, after removal of the protecting group and acetylation, the pheromone **7** or, after a simple deprotection step, the pheromone **9** (98% stereoisomeric purities, by GLC analysis).

The following synthesis of bombykol **3** is representative of our methodology for the preparation of *E-Z* dienic pheromones. Phenylthioacetylene (0.8 g, 6 mmol) in ether (40 ml) was added to an ethereal solution of *Z*-dipentenyl cuprate[5] (80 ml, 8 mmol), under nitrogen at -50°C. After the addition, the mixture was slowly brought at room temperature and the reaction was monitored by GLC analysis until the starting material was consumed. After reaction completion (2h), the mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated, giving the almost pure product **2**, which was characterized by GC/MS spectrometry analysis[17] and used as such in the next step. The stereochemistry of the double bonds was ascertained from the ^{1}H-NMR coupling constants between the vinylic protons[17]. The coupling reaction was performed by adding a 0.5 M solution of the functionalized Grignard reagent, (prepared from 9-bromononan-1-ol, protected as an ethoxyethyl ether), in Et_2O/THF 1/1 (12.6 ml, 6.3 mmol) to a stirred suspension containing dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II) (0.1 g, 0.19 mmol) and (1*E*,3*Z*)-1-phenylthio-1,3-heptadiene **2** (1.0 g, 4.9 mmol) in anhydrous Et_2O (50 ml) at room temperature under nitrogen. After stirring for 8h, the mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined extracts were washed with 10% aqueous NaOH and with H_2O and dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude product, dissolved in 10 ml of MeOH, was added to an aqueous solution (3 ml) of p-toluenesulphonic acid (0.02 g). After stirring at 0°C for 3h, the solvent was removed under reduced pressure and 50 ml of ether were added along with 30 ml of H_2O. The aqueous layer was extracted twice with ether and the combined organic phases were washed with aqueous $NaHCO_3$, with water, and then dried over Na_2SO_4. After evaporation of the solvent, the crude residue was distilled at 118-119°C/

Scheme 2 *Synthesis of E-Z dienic pheromones*



Scheme 3 *Synthesis of Z-E dienic pheromones*



$4\cdot10^{-4}$ mm Hg[4c] to afford 0.93 g of pure bombykol **3** in 80% yield[18].

In conclusion, the procedure described here should provide a highly stereospecific route to double stereodefined conjugated dienes starting from a common intermediate. Moreover, taking into account the simplicity of the operations involved and the relatively high overall yields, we believe that the present method compares favourably with alternative methodologies.

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17) ^{1}H-NMR spectra were recorded on a Varian XL 200, 200 MHz, in $CDCl_3$ as solvent. GC/mass-spectrometry analysis were performed on a Hewlett-Packard 5890A Gas Cromatograph equipped with HP-17 capillary column, 25 m, and Hewlett-Packard Mass Selective Detector MSD 5970B.
   (1*E*,3*Z*)-1-Phenylthio-1,3-heptadiene **2**, ^{1}H-NMR data: δ 0.94 (t, 3H, J=7.24 Hz), 1.34-1.50 (m, 2H), 2.10-2.22 (m, 2H), 5.45 (dt, 1H, J=7.70 Hz, $J_{3,4}$=10.8 Hz, **4-H**), 6.07 (dd, 1H, $J_{2,3}$=10.8 Hz, $J_{3,4}$=10.8 Hz, **3-H**), 6.36 (d, 1H, $J_{1,2}$=14.9 Hz, **1-H**), 6.72 (dd, 1H, $J_{1,2}$=14.9 Hz, $J_{2,3}$=10.8 Hz, **2-H**), and 7.20-7.45 ppm (m, 5H). Mass spectral data: *m/e* 204 (M^+, 100), 175 (40), 161 (11), 109 (30), 95 (52), 77 (21).
18) The spectral data of compounds **5** and **7** were in good agreement with those of authentic commercial samples and the spectra of pheromones **3** and **9** matched those previously reported[4c,5]. All new compounds gave consistent ^{1}H-NMR and MS spectral characteristics.

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