# A STEREOSELECTIVE SYNTHESIS OF A CIS, CIS CONJUGATED DIENOL, A CANDIDATE PHEROMONE

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There has been much interest recently focussed on the synthesis of geometrically pure conjugated diene alcohols, aldehydes and esters useful as sex pheromones and candidate sex attractants.[1,2] A recent communication[3] on the synthesis of all four geometrical isomers of some conjugated dienols by four different Wittig reactions prompts us to report our results on the synthesis of a *cis*, *cis* conjugated dienol, as the reported synthesis of this type of isomer yielded product of low geometrical purity.[3] We describe below our stereoselective synthesis of a *cis*, *cis* conjugated dienol

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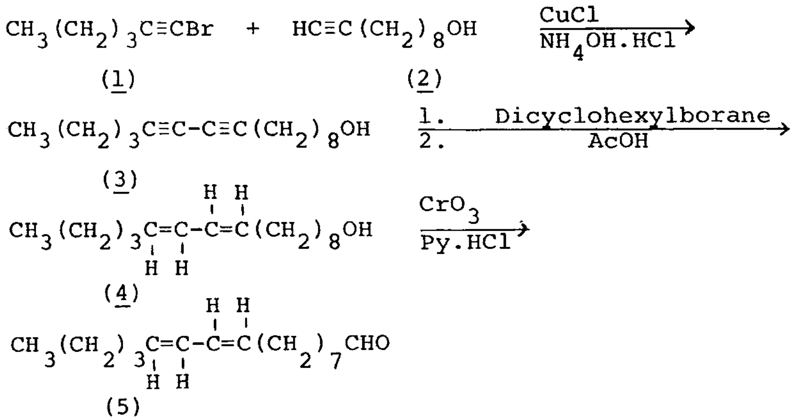
by a simple alternative route involving a Cadiot-Chodkiewicz coupling reaction and a dialkylborane reduction as the key steps.

A methanolic solution of 1-bromo-1-hexyne (1)[4] and 9-decyn-1-ol (2)[5] was treated with cuprous chloride and hydroxylamine hydrochloride in a slightly modified version of the Cadiot-Chodkiewicz coupling reaction[6] to give 9,11-hexadecadiyn-1-ol (3) in 51% yield as outlined in the Scheme. The conjugated diyne (3) can be stereoselectively reduced to cis,cis-9,11-hexadecadien-1-ol (4) by treatment with two equivalents of dicyclohexylborane by the procedure described by Zweifel and Polston[7] but slightly modified as described below. Compound (4) can be readily oxidized to cis,cis-9,11-hexadecadienal (5) by chromium trioxide and pyridinium chloride.[8] Analysis of (4) and (5) by vpc showed that both compounds were greater than 94% pure and hence a rapid method of obtaining pure cis,cis conjugated dienols and derivatives has been achieved.



$$CH_3(CH_2)_3C\equiv CBr \quad + \quad HC\equiv C(CH_2)_8OH \quad \xrightarrow[NH_4OH.HCl]{CuCl}$$

(1) (2)

$$CH_3(CH_2)_3C\equiv C\text{-}C\equiv C(CH_2)_8OH \quad \xrightarrow[2.\qquad AcOH]{1.\quad Dicyclohexylborane}$$

(3)

$$CH_3(CH_2)_3\underset{H}{C}=\underset{H}{C}-\overset{H}{C}=\overset{H}{C}(CH_2)_8OH \quad \xrightarrow[Py.HCl]{CrO_3}$$

(4)

$$CH_3(CH_2)_3\underset{H}{C}=\underset{H}{C}-\overset{H}{C}=\overset{H}{C}(CH_2)_7CHO$$

(5)

Both (4) and (5) were tested against various Lepidopteran pests.

Surprisingly, the Cadiot-Chodkiewicz coupling reaction had not previously been applied to the synthesis of sex pheromones and yet provided an ideal rapid method of obtaining the stereochemically pure cis, cis conjugated dienols. Attempts to adapt our solid phase syntheses of insect sex attractants[9] to the synthesis of conjugated dienols by the above sequence failed.

## EXPERIMENTAL

A Bausch and Lomb Abbé 3L refractometer was used to record the refractive indices. Infrared spectra were recorded on a Unicam SP1000 ir spectrophotometer as neat films between NaCl discs unless otherwise specified. Nuclear magnetic resonance spectra were recorded on a Varian EM360 spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on a Perkin-Elmer-Hitachi RMU6E mass spectrometer, operated at 70eV. Vapour phase chromatograms (vpc) were obtained using OV-101 and Hi-eff 8BP (cyclohexanedimethanol succinate) columns at 175° and 190°C respectively.

Experiments involving reactive organometallic reagents were carried out under argon. The tetrahydrofuran (THF) was refluxed over $LiAlH_4$ for 4 hr. and distilled under argon. It was freshly distilled. The hexamethylphosphoric triamide (HMPT) and other solvents were dried and distilled. Solvents were removed on a rotary evaporator. Melting and boiling points are uncorrected. Microanalyses were performed by G. Gygli in Toronto. Spectral and analytical data are given for all new compounds and for known compounds where data are unreported.

### 9,11-Hexadecadiyn-1-ol (3)

To the stirred mixture of a 33% solution of propylamine in water (10 ml), cuprous chloride (25 mg) and hydroxylamine hydrochloride (1.8 g) was added rapidly a solution of (2) (4.62 g, 30 mmole) in methanol (50 ml). The mixture was cooled to $0^{\circ}$ and a methanolic solution of (1) (5.1 g, 32 mmole) was added dropwise with vigorous stirring. The temperature rose to $30^{\circ}$. An excess of hydroxylamine hydrochloride should be kept to maintain the copper in the reduced state (small portions of $NH_4OH.HCl$ were added from time to time). The reaction mixture was stirred at $40^{\circ}$ for 3 hr, then treated with potassium cyanide (0.5 g), diluted with cool water (300 ml) and extracted with ether (3 x 50 ml). The ether extract was washed with water (25 ml), dried ($Na_2SO_4$) and the ether evaporated. The resulting residue was distilled through a short Vigreux column to give: fr.I b.p. 50-90/0.02 mm, 2.5 g, $n_D^{26}$ 1.4563; fr. II b.p. $90\text{-}170^{\circ}/0.02$, 1.0 g, $n_D^{26}$ 1.4630; fr.III b.p. $170\text{-}172^{\circ}/0.02$, 3.15 g, $n_D^{26}$ 1.4980. Chromatography of fr.I on silica gel using benzene as eluant gave 1.0 g of the dimer of (1), 5,7-dodecadiyne. Elution with benzene:ether (90:10) gave 1.0 g of (2). The spectral data of these samples were identical with those of an authentic sample. Chromatography of fr.II on a silica gel column, using benzene:ether (85:15, 80:20) as eluant gave 0.5 g of pure (3). The fraction III represented almost pure (3) (total yield 3.65 g, 51%). Rapid chromatography of the yellow product on silica gel using benzene:ether (85:15, 80:20) as eluant gave pure (3) as a slightly yellow thick oil $n_D^{25}$ 1.4985; IR: 3340 (O-H), 2190, 2280 ($C\equiv C\text{-}C\equiv C$); 1060 (C-O); NMR $\delta$: 3.66 (t, 2, J = 8 Hz, $C\underline{H}_2O$), 2.2 (t, 4, J = 7 Hz, $C\underline{H}_2$-

C≡C-C$\underline{H}_2$), 1.7-1.15 (m, 17, aliphatic H and 1H OH), 0.92 (t, 3, J = 6 Hz, C$\underline{H}_3$). MS: 234 ($M^+$); UV: (ethanol) $\lambda_{max}$ (214, 226, 241, 254 nm (ε 486, 410, 429, 275). Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.36; H, 11.50.

## (Z,Z)-9,11-Hexadecadien-1-ol (4)

To the dicyclohexylborane (11 mmole) in 25 ml THF was added at -5° to -2° a solution of (3) (0.6 g, 2.5 mmole) in 10 ml of THF under argon. The suspension was stirred at -5° to 0° for 2 hr. and then the mixture was allowed to warm slowly to room temperature. During stirring for an additional 2 hours at room temperature the precipitate of the dicyclohexylborane disappeared. To the colourless solution was added glacial acetic acid (2.5 ml) and the mixture was stirred at 40 to 50° overnight. Treatment of the cool mixture with 6N sodium hydroxide (8.5 ml) and dropwise adding 30% hydrogen peroxide (2.6 ml) at 35° oxidized the dicyclohexylborinate completely. The residue was extracted with ether (100 ml) and the etheral solution was washed with water, dried and the solvent removed to give 1 g of crude product, which was chromatographed on silica gel. Elution with benzene:ether (95:5 and 92.5:7.5) gave 0.5 g (82%) of alcohol 4. Distillation gave pure 4; b.p. 145-146°/0.02 mm; $n_D^{24}$ 1.4769 as a clear liquid which crystallized in refrigerator; UV: (ethanol) $\lambda_{max}$ 237 nm (ε 29.100), 230 nm (sh.26.600); MS: 238 (34) ($M^+$); 220 (13) ($M^+$-$H_2O$), 67, 81 (100); IR: 3380 (O-H), 1780 (w), 1662 (w), 1600 (s) (C=C conjugated), 1060 (C-O), 730 (*cis* CH=CH); NMR δ: 6.32-6.20 (m, 2) and 6.52-6.46 (m, 2 $\underline{H}$C=C$\underline{H}$ conjugated) 3.68 (t, 2, J = 6 Hz, $CH_2O$), 2.2 (m, 4, $C\underline{H}_2$-$(CH=CH)_2$-$C\underline{H}_2$), 1.88-1.08 (m, 19, 18 aliphatic H and 1H OH), 0.88 (t, 3, J = 5 Hz, $C\underline{H}_3$-$CH_2$).

Anal. Calcd. for $C_{10}H_{30}O$: C, 80.60; H, 12.68. Found: C, 80.74; H, 12.83.

Analysis of (4) by vpc on two columns known to separate geometrical isomers of conjugated dienes showed that (4) was greater than 94% of the pure Z,Z isomer.

### (Z,Z-9,11-Hexadecadien-1-al (5)

Chromium trioxide (110 mg, 11 mmole) and pyridinium chloride (125 mg, 1.1 mmole) was added to the stirring solution of methylene chloride and the mixture stirred for 10 min. The alcohol 5 (100 mg, 0.42 mmole) in 5 ml dichloromethane was added in one portion (temperature rose at 35°) and the mixture was stirred an additional hr. at room temperature. The reaction mixture was poured into a solution of sodium bicarbonate (5%, 30 ml). The organic layer was separated, the water extracted with methylene chloride (2 x 25 ml) and the combined extract was washed with water and passed through a bed of alumina (act III, 5 g). The alumina took out all coloured impurities. The solvent evaporated to give 100 mg of crude product. The aldehyde 5 was rapidly chromatographed on a silica gel column (20 g) eluting with benzene:ether (95:5) to give 7.0 mg of pure aldehyde, which was immediately sealed in ampoules under argon. IR: 2720 (CHO) 1735 (C=O), 720 (cis CH=CH); UV: (ethanol) $\lambda_{max}$ 237 nm (27700), 230 (25800); NMR $\delta$: 9.85 (t, 1, J = 1 Hz, $C\underline{H}O$), 6.3-6.1 (m, 2), 5.5-5.3 (m, 2) ($\underline{H}C=C\underline{H}$-conjugated) 2.5-1.9 (m, 4, $C\underline{H}_2(CH=CH)_2C\underline{H}_2$), 1.9-1 (m, 14, $(C\underline{H}_2)_7$), 0.9 (t, 3, J = 6 Hz, $C\underline{H}_3CH_2$). MS: 238 (34) ($M^+$), 202 (25) ($M^+$-CHO): 193 (41) ($M^+$-$CH_2$CHO); 67 (100).

*Anal*. Calcd. for $C_{10}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.59; H, 12.45.

Analysis of (5) as before showed that (5) was also greater than 95% of the pure Z,Z isomer and hence no isomerization occurred in the oxidation step.

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