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A simple synthesis of (±)-2,6-dimethylocta-5(*Z*),7-diene-4-ol and its attractant activity for the bark beetle *Ips typographus*

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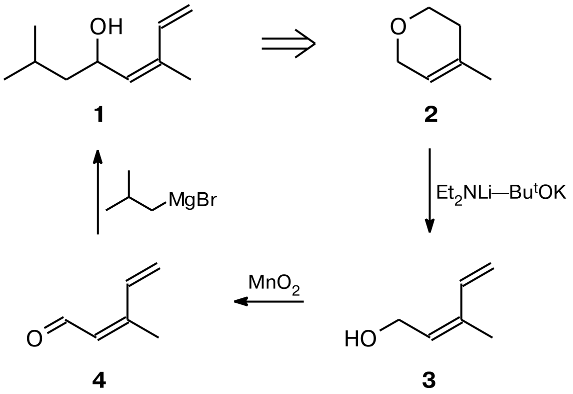
A simple method for the synthesis of (±)-2,6-dimethylocta-5(*Z*),7-diene-4-ol possessing a high pheromone activity for the bark beetle *Ips typographus* was developed.

Key words: (±)-2,6-dimethylocta-5(*Z*),7-diene-4-ol, sex attractant, bark beetle (*Ips typographus*).

As reported previously,[1] the low-molecular-weight component isolated from the bore meal of the bark beetle (*Ips typographus*), (±)-2,6-dimethylocta-5(*Z*),7-dien-4-ol (**1**), exhibits a high pheromone activity with respect to this dangerous forest pest. The biological activity of a composition based on a synthetic specimen of this compound proved to be higher (in one series, almost twice) than the activity of a reference mixture consisting of methylbutenol, (*S*)-(*Z*)-verbenol, and ipsdienol.[1] This communication describes a new facile route to compound **1** starting from a readily available industrial intermediate, 4-methyl-5,6-dihydro-2*H*-pyran (**2**)[2] (Scheme 1).

Scheme 1



The choice of compound **2** as a starting material was made taking into account its stereoselective conversion[3] into dienol **3** on treatment with a mixture of lithium *N*,*N*-diisopropylamide (LDA) with Bu^tOK. Dienol **3** can be oxidized[4] to the corresponding aldehyde **4**, a key compound in the protocol we propose for the synthesis of the target dienol **1**.

In the realization of this synthesis, we substantially modified the previously described[3] procedure for the scission of dihydropyran **2** to alcohol **3**, which included an experimentally inconvenient procedure for the preparation of an unstable solution of Bu^nLi in tetrahydrofuran, by replacing the solvent (hexane). We made use of a known procedure for the preparation of lithium dialkylamides (including LDA) by direct reaction of dialkylamines with metallic lithium in the presence of electron acceptors (for example, methylstyrene).[5] Treatment of dihydropyran **2** with a solution of Et_2NLi prepared in this way in the presence of a catalytic amount of Bu^tOK gave alcohol **3** (yield 82%) containing ~3% of a 2(*E*)-isomer as an impurity (^1H NMR data) (*cf.* Ref. 3). Oxidation of this specimen of alcohol **3** with excess MnO_2 gave aldehyde **4** in good yield and with approximately the same content of the isomer. In the final stage of the synthesis, the Grignard reaction of aldehyde **4** with Bu^iMgBr afforded the target dienol **1** in 61% yield (the overall yield over three steps is 38%). The content of the corresponding impurity with the *trans*-trisubstituted double bond increased to ~6%, apparently, due to partial isomerization of the starting aldehyde **4** under the condensation conditions.

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The structures of the obtained compounds **1**, **3**, and **4** were confirmed by comparing their physicochemical characteristics with those published previously. The contents of the stereoisomer impurities in the samples of these dienes were determined by measuring the integral intensities of the signals for the methine protons (dd) of the CH_2=CH fragment in the ^{1}H NMR spectra at δ 6.77 (**1**), 6.71 (**3**), and 7.34 (**4**) (the major product) and those at δ 6.33, 6.35, and 6.40 (the minor components), respectively.

The biological activities of compound **1** were studied in the Moscow and Leningrad Regions in May to August, 2003. The first series of experiments was performed to compare the efficiency of two compositions (*A* and *B*) of dienol **1** with (–)-(*Z*)-verbenol and 2-methylbut-3-en-2-ol in ratios of 3 : 70 : 1500 (*A*) and 0.5 : 70 : 1500 (*B*) in the attraction of the *Ips typographus* beetles. Both mixtures were injected into a dispenser and tested in barrier traps in five experiments. The tests revealed an increase in the insect attraction with a decrease in the dosage of compound **1** typical of substances with marked pheromone activities (Table 1).

The next series of tests was performed to compare the efficiency of composition *B* with that of the known preparation Vertenol[6] (2-methyl-6-methyleneocta-2,7-dien-4-ol (**5**)[7] : (–)-(*Z*)-verbenol : 2-methylbut-3-en-2-ol = 6.7 : 70 : 1500). Both mixtures were tested in three experiments. Since the results of the experiments depend appreciably on the location of traps (differences in the illuminance, wind direction, and so on), the positions of dispensers in the traps were exchanged in pairs. It can be seen from the data obtained (Table 2) that the mixture containing dienol **1** instead of dienol (**5**) is not almost inferior in activity. Since the required amount of dienol **1** in the mixture is an order of magnitude lower, it is more economical to use this compound, which is more readily available than dienol **5**, for both observation and control over the bark beetle.

Experiment

^{1}H NMR spectra of solutions in $CDCl_3$ were recorded on a Bruker AC-200 spectrometer with respect to the residual proton signal of the solvent (δ 7.27). Column chromatography was performed on SiO_2 (40/100; Chemapol).

Table 1. Number of beetles caught from May 8 to 23, 2003 (Moscow Region)

Test date	Composition *A*		Composition *B*	
	total	average per trap	total	average per trap
May 8	304	60.8	409	81.8
May 12	998	199.6	1889	377.8
May 16	2925	585.0	4130	826.0
May 20	657	131.4	842	168.4
May 23	1303	260.6	1673	334.6

Table 2. Number of beetles caught from July 2 to August 5, 2003, at three territories of the Leningrad Region

Test date and place	Composition *B*		Vertenol	
	total	per trap per 24 h	total	per trap per 24 h
2.07—14.07 Dolgozero	776	74.0	961	80.1
18.07—26.07 Yandozero	74	8.2	81	9.0
2.07—14.07 Vepsky Forest	788	112.6	910	130.0

Activated MnO_2 was prepared by a known procedure.[8]

Commercial methylstyrene, diethylamine, and potassium *tert*-butoxide (Aldrich) were used. The solvents were purified by standard procedures.

3-Methylpenta-2(*Z*),4-diene-1-ol (3). Methylstyrene (3.7 g, 31.5 mmol) and Et_2NH (4.59 g, 63 mmol) were added at 20 °C under dry argon to a suspension of finely cut lithium foil (0.42 g, 60 mmol) in 30 mL of THF. The reaction mixture was stirred for 2 h at a temperature not exceeding 30 °C (*cf.* Ref. 5). The resulting solution of Et_2NLi was cooled to –60 °C, and Bu^tOK (0.56 g, 5 mmol) and dihydropyran **2** (4.90 g, 50 mmol) were added. The reaction mixture was stirred for 2 h at –50 °C and treated with 150 mL of Bu^tOMe and 20 mL of water. The organic layer was separated, washed with 5% HCl and water, dried with Na_2SO_4, and concentrated under atmospheric pressure. The residue was chromatographed on 150 g of SiO_2, the products being eluted first with light petroleum (b.p. 40—70 °C) and then with a pentane—ether mixture (1 : 1, v/v) to give 4.02 g (82%) of dienol **3** as a colorless liquid, b.p. 60—61 °C (7 Torr), n_D^{20} 1.4950 (*cf.* Ref. 3). ^{1}H NMR, δ: 1.83 (br.s, 3 H, Me); 1.96 (br.s, 1 H, OH); 4.23 (d, 2 H, CH_2O, J = 5.3 Hz); 5.12 (d, 1 H, *trans*-C(5)H, J = 7.0 Hz); 5.25 (d, 1 H, *cis*-C(5)H, J = 11.8 Hz); 5.55 (br.t, 1 H, C(2)H, J = 5.3 Hz); 6.71 (dd, 1 H, C(4)H, J = 7.0 Hz, J = 11.8 Hz).

3-Methylpenta-2(*Z*),4-dien-1-al (4).[4] Manganese dioxide (36 g, 0.41 mol) was added to a solution of alcohol **3** (3.0 g, 30.6 mmol) in 150 mL of CH_2Cl_2 and the suspension was vigorously stirred for 5 h at 20 °C and filtered. The precipitate was washed on the filter with CH_2Cl_2 (3×120 mL). The filtrate was concentrated under atmospheric pressure and the residue was distilled *in vacuo* to give 2.23 g (76%) of aldehyde **4** as a light-yellow liquid, b.p. 57—58 °C (19 Torr), n_D^{20} 1.5210. ^{1}H NMR, δ: 2.04 (s, 3 H, Me); 5.54 (d, 1 H, *trans*-C(5)H, J = 7.3 Hz); 5.63 (d, 1 H, *cis*-C(5)H, J = 12.2 Hz); 5.85 (br.d, 1 H, C(2)H, J = 5.7 Hz); 7.34 (dd, 1 H, C(4)H, J = 7.3 Hz, J = 12.2 Hz); 10.31 (d, 1 H, CHO, J = 5.7 Hz).

(±)-2,6-Dimethylocta-5(*Z*),7-dien-4-ol (1). A solution of aldehyde **4** (2.16 g, 22.5 mmol) in 10 mL of THF was added at 0 °C under dry argon over a period of 5 min to a stirred solution of Bu^iMgBr, prepared from Mg (1.04 g, 43 mmol) and Bu^iBr (4.93 g, 36 mmol) in 50 mL of THF in 2 h at 25—30 °C. The reaction mixture was heated to 20 °C, stirred for 2 h, and treated with 20 mL of a saturated aqueous solution of NH_4Cl at 0 °C. The organic layer was separated, washed with water and brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (80 g) using a mixture of light petroleum (b.p. 40—70 °C) and Bu^tOMe (4 : 1, v/v) as the eluent to give 2.12 g (61%) of dienol **1** as a colorless liquid, b.p. 49—50 °C (1 Torr), n_D^{20} 1.4792. ^1H NMR, δ: 0.91, 0.94 (both d, 6 H, 2 Me, J = 3.8 Hz); 1.29, 1.49, 1.70 (all m, 3 H, CH, CH_2); 1.78 (br.s, 1 H, OH); 1.85 (br.s, 3 H, Me); 4.63 (dd, 1 H, HCO, J = 3.5 Hz, J = 5.0 Hz); 5.13 (d, 1 H, *trans*-C(8)H, J = 6.5 Hz); 5.26 (d, 1 H, *cis*-C(5)H, J = 11.2 Hz); 5.34 (br.d, 1 H, C(5)H, J = 5.0 Hz); 6.77 (dd, 1 H, C(7)H, J = 6.5 Hz, J = 11.2 Hz).

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