## Chemistry of Natural Compounds and Bioorganic Chemistry

## Synthesis of 7E, 9Z-dodecadienyl acetate, the sex pheromone of *Lobesia botrana* Shiff

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Two syntheses of 7*E*,9*Z*-dodecadienyl acetate from 1,3-butadiyne were carried out using either 2*E*,4*Z*-heptadienyl acetate or 1-bromo-3*E*,5*Z*-octadiene as the key intermediates. The latter underwent organocopper cross-coupling with the respective complementary Grignard reagents (prepared from the corresponding 1-*tert*-butoxy- $\omega$ -chlorohydrins) as alkylating agents.

Key words: 7E,9Z-dodecadienyl acetate, synthesis; organocuprates, cross-coupling; 2E,4Z-heptadienyl acetate; 1-bromo-3E,5Z-octadiene; 1,3-butadiyne.

The sex pheromone of *Lobesia botrana* Shiff (Lepidoptera : Tortricidae), 7E,9Z-dodecadienyl acetate (DDDA, 1), is an ecologically harmless means of protecting grape vines. The steady interest attracted to this pheromone in Russia and abroad is shown by the fact that more than 20 procedures for its synthesis have been published since its first isolation and identification<sup>1,2</sup> (see the reviews<sup>3-5</sup>).

The synthetic approaches to E,Z-dienic pheromones based on the use of organophosphorus compounds,<sup>5-12</sup> organoboranes,<sup>13-15</sup> and complexes of transition metals<sup>16-21</sup> have been developed rather well. Acetylenic intermediates have found especially wide use for the synthesis of stereochemically pure conjugated dienes in the last 3-5 years; this has led to the appearance of several new methods for their preparation.<sup>22-26</sup>

Although there exist plenty of methods for the synthesis of pheromone 1, the latter still remains difficult to obtain, and its production is relatively expensive. The methods known for its synthesis are rather laborious in technological respects, they consist either of reagents that are hard to obtain, or of procedures that cannot be reproduced on a larger scale.

With the aim of obtaining significant amounts of DDDA\*, we undertook the optimization of the chemical schemes proposed for the synthesis of the key in-

\* DDDA = 7,9-dodecadienyl acetate.

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## Scheme 1



a. Li/liq.NH<sub>3</sub>; b. EtI/DMSO; c. CH<sub>2</sub>O/DMSO; d.  $\overset{H_2C-CH_2}{\circ}$ /DMSO; e. LiAlH<sub>4</sub>/Et<sub>2</sub>O; f. LiAlH<sub>4</sub>/THF; g. Zn(Cu)/*i*-PrOH; b. Ac<sub>2</sub>O-DMAP/Et<sub>2</sub>O; *i*. TsCl, Py; *j*. NaBr/Me<sub>2</sub>CO; k. CBr<sub>4</sub>-Ph<sub>3</sub>P/CH<sub>2</sub>Cl<sub>2</sub>; *l*. Mg/THF, CuI; m. Mg/THF-Et<sub>2</sub>O, CuCN-LiCl; n. MeOH/TsOH; o. EtOH/H<sub>2</sub>SO<sub>4</sub>; p. Ac<sub>2</sub>O-FeCl<sub>3</sub>/Et<sub>2</sub>O.

termediates involved in the preparation of the pheromone (Scheme 1). For this purpose we chose 1,3-butadiyne (2), which is formed in the purification of pyrolytic acetylene (10-12 % diacetylene in water—ammonia) and is usually burnt. The syntheses of type 1 *E*,*Z*-dienes from diyne 2 have not found wide use, and have been described in outline only.<sup>27</sup>

The synthesis of diacetylenic derivatives 4 and 5 starting from diacetylene was carried out by consecutive alkylation with ethyl iodide and hydroxyalkylation with paraform or ethylene oxide. It turned out that the 1,3-diynes, diacetylene and the intermediate 1,3-hexadiyne, which are very inconvenient in technological respect, could be used without purification by distillation, which led to losses due to the high lability of these compounds.

In order to optimize the conditions of these steps we studied several methods of alkylation: by means of sodium and lithium amides in liquid ammonia, in the presence of strong anionite AV-17-8P in the OH<sup>-</sup>-form, or using the Iotsitch reagent. Some modifications were introduced into the procedure for synthesizing alcohols 2 and 5, which allowed us to obtain these products in a stable yield of up to 12-18 % (over the two steps) from 1,3-butadiyne (the optimal reagents are shown in the Scheme).

The key stage of the synthesis is the construction of the hydrocarbon chain. Cross-coupling of electrophiles with organocopper compounds<sup>29</sup> is most widely used for this purpose. We used E, Z-dienic allylic acetate (8) and homoallylic bromide (12) as the hydrocarbon fragments of DDDA. The componds specified were easily obtained by standard methods that involved (a) the regioselective trans-reduction of the triple bond adjacent to the hydroxyl by means of  $\text{LiAlH}_4$ ;<sup>30</sup> (b) the cis-reduction of the triple bond in conjugated enynes 6 and 9 (in this case the best results were obtained with an excess of activated Zn, which was prepared using the procedure in ref. 31 in isopropyl alcohol at  $60-80^{\circ}$ C); (c) the subsequent functionalization of compounds 7, 10, and 11 thus formed. The derivatives obtained proved to be stereochemically pure after chromatography on SiO<sub>2</sub>. They contained not less than 96 % of the corresponding E, Z-isomer according to the capillary GLC and <sup>1</sup>H NMR spectral data.

For the preparation of DDDA from organomagnesium compounds, O-protected  $\omega$ -chlorohydrins in the form of

tetrahydropyranyl (13) or *tert*-butyl ethers (14) and (15) were used in the reaction. The coupling of acetate 8 with the Grignard reagent prepared from compound 13 (in a 1:3 ratio) activated with CuI, gave the target product 16 in 35-50 % yield. However, this method did not ensure stable reproducible results, probably due to the Wurtz reaction, which is difficult to control, accompanying the formation of the Grignard reagent.\*

The interaction of acetate 8 with *tert*-butoxy-substituted magnesium chloride (14a) occurs more efficiently. In this case, due to the stability of the reagent 14a, the yields of the target product (17) vary from 50 to 70 % depending on the solvent, temperature, reaction time, and the nature of catalyst. As no considerable difference was obseved for the reaction carried out in the tetrahydrofuran—ether mixture and in pure tetrahydrofuran, it was easier to use an ethereal solution of the Grignard reagent 14a and tetrahydrofuran as the solvent for acetate 8.

In both cases the reaction of allylic acetate 8 with CuI as a catalyst occurs non-stereospecifically and results in the formation of a mixture of 7E,9Z and 7E,9E isomers of the ethers (16) and (17) (GLC and <sup>1</sup>H NMR spectral data) in  $\approx 3:1$  ratio.

The other, more selective method for the synthesis of dienic ether 17 (>92 % of the 7*E*,9*Z*-isomer) is also based on the organocuprate method. In this case, in the presence of CuCN—LiCl as the catalyst, the homoallylic bromide 12 couples with the Grignard reagent obtained from chloride 15 in a yield of up to 60 %. This is the most convenient and definite approach to *E*,*Z*-unsaturated diolefins with a controlled and, above all, unambiguous configuration.

The transformation of ethers 16 and 17 into the target diene 1 occurs smoothly by ordinary steps through the corresponding alcohol 18; in the case of *tert*-butyl ether 17 this reaction occurs in one stage under mild catalysis conditions with FeCl<sub>3</sub> under the action of acetic anhydride.<sup>24</sup>

This work resulted in the elaboration of a method for the synthesis of DDDA starting from the accessible raw material, diacetylene. The method proposed is more acceptable preparatively and allows a wide range of tests aimed at the practical application of this pheromone to be carried out.

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\*Contradictory data on its formation are given in literature (e.g., see ref. 31).