

# The Synthesis of (Z)-8-Dodecen-1-ol and its Acetate, Pheromone Components of the Oriental Fruit Moth (*Grapholita molesta*)

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**The two main sex pheromone components of the Oriental fruit moth (*Grapholita molesta*), viz. (Z)-8-dodecen-1-ol and its acetate, have been synthesized from (Z,E,E)-1,5,9-cyclododecatriene in approximately 15 % overall yield.**

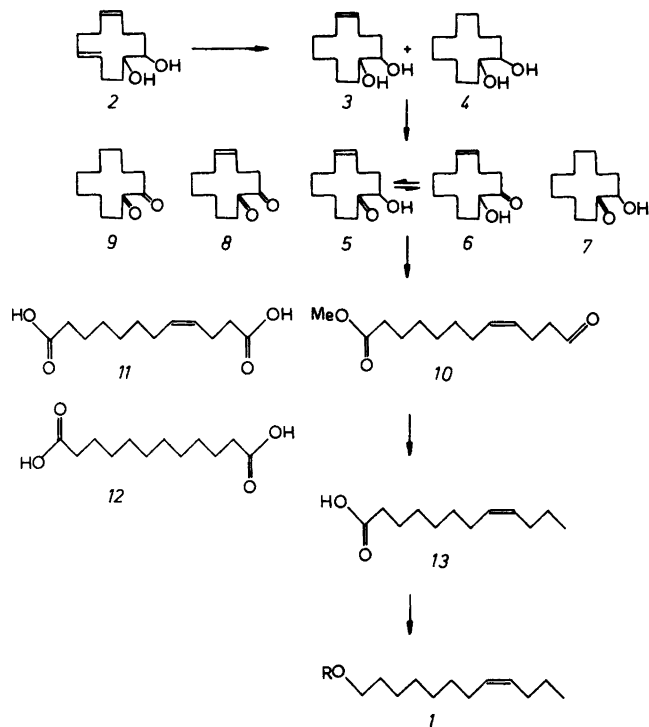
The Oriental fruit moth (*Grapholita molesta*) is a destructive pest to fruit orchards in many parts of the world. Roelofs and co-workers<sup>1</sup> isolated a compound assumed to be the sex pheromone and established its structure as (Z)-8-dodecen-1-yl acetate (*1a*). A synthetic sample of *1a* was very active in field tests.<sup>2</sup> Subsequently, other components were identified,<sup>3</sup> and at present the sex pheromone is believed to consist of *1a*, (Z)-8-dodecen-1-ol (*1b*), (E)-8-dodecen-1-yl acetate and dodecan-1-ol in a ratio of 100:30:7:6. Compound *1a* has also been found to be a major pheromone component of a number of related insect species.<sup>4</sup>

Several syntheses of the main component *1a* have been described,<sup>1,5</sup> and the other pheromone components are either on the route to or can easily be derived from this compound. Most of these synthetic schemes use either hydrogenation of a triple bond or the Wittig reaction for introducing the *cis* double bond. In the present paper we describe a synthesis of *1a* starting from the inexpensive (Z,E,E)-1,5,9-cyclododecatriene (CDT).

The general idea behind our synthetic strategy was to use as starting material a compound containing a *Z* double bond which should not be affected through the sequence of reactions leading to the final product. The *Z,E,E* isomer of CDT should lend itself well in this respect because the literature reveals several examples of addition reactions that show a substantial preference for the *E* double bonds.<sup>6</sup> Epoxidation gives with high degree of selectivity the *trans* mono-epoxide<sup>7</sup> which was converted to the corresponding diol. A similar selectivity has been obtained from oxidations with permanganate and osmium tetroxide.<sup>8</sup> Hence, both *trans*- and *cis*-(*E*)-5,(*Z*)-9-cyclododecadiene-1,2-diol (**2**) were readily available from CDT and they were transformed into *1a* as outlined in Scheme 1.

Catalytic hydrogenation of the diols **2** using a variety of catalysts and conditions gave a mixture of products and the selectivity was quite unsatisfactory. This is in accordance with results obtained with CDT itself under similar conditions. On the other hand, reduction of CDT with diimide had been reported<sup>9</sup> to yield practically pure (Z)-cyclododecene.

The reduction of *trans*-**2** with diimide afforded essentially a 3:1 mixture of *trans*-(Z)-5-cyclododecene-1,2-diol (**3**) and *trans*-cyclododecane-1,2-diol (**4**),<sup>10</sup> respectively, in a



Scheme 1. a, R=CH<sub>3</sub>CO; b, R=H.

combined yield of 95 %. A similar product composition was obtained, in 87 % yield, from *cis*-2. Diimide was generated by oxidation of hydrazine hydrate with hydrogen peroxide using cupric sulfate as catalyst.<sup>9</sup> The other methods<sup>11</sup> tried were found less convenient also with respect to selectivity and yield.

The direct analysis of the diols by gas chromatography (GLC) was not successful. Hence, aliquotes of the reaction mixtures were oxidized with lead tetraacetate prior to analysis. Good separation of the dialdehydes corresponding to the diols 3 and 4 was obtained on a 25 m capillary column coated with SP1000. Separation of the diols on a preparative scale was equally unsuccessful and we proceeded with the mixture anticipating the separation of products derived from 4 at a later stage in the synthesis.

Oxidation of the diols to the corresponding  $\alpha$ -hydroxy ketones was achieved with several reagents with variable success. The best result was obtained with the *N*-chlorosuccinimide-dimethylsulfide complex.<sup>12</sup> The product consisted mainly of the isomeric  $\alpha$ -hydroxyketones 5 and 6 together with 2-hydroxycyclododecanone (7) but small amounts of the diketones 8 and 9 were formed as well. The latter was separated by column chromatography. GLC analyses were performed successfully on the product mixtures. The major component of the mixture was crystalline and was obtained pure after several crystallizations. It was not possible to determine the structure 6 from spectral information alone, but combined with results from oxidative degradations it was established unambiguously. The ratio of the regioisomers 5 and 6 was not reproduceable except care was taken to avoid acid during work-up. Under such conditions a 3:1 ratio in favour of the unwanted isomer 6 was

obtained. However, treatment of this mixture with either acid or base caused isomerization to a 93:7 mixture of 5 and 6, respectively. For the preparation of 5, it was actually advantageous to oxidize the diols to the diketones 8 and 9 with dimethylsulfoxide-dicyclohexylcarbodiimide<sup>13</sup> and subsequently reduce the crude product with zinc in aqueous dimethylformamide.<sup>14</sup> The reaction mixture was stirred with powdered KOH at room temperature for 90 min. and worked up to a product consisting of essentially a 3:1 mixture of the  $\alpha$ -hydroxyketones 5 and 7 in 81 % overall yield based on the diols. Evidently, the isomer 6 is kinetically preferred, while 5 is sufficiently more stable thermodynamically to become the almost exclusive product by simple acid-or base-catalyzed equilibration.

The mixture of  $\alpha$ -hydroxyketones was oxidized with lead tetraacetate in benzene-methanol to the corresponding oxoesters. The saturated oxoester; viz. methyl 12-oxododecanoate, was separated from the crude mixture as a clathrate with urea,<sup>15</sup> leaving behind methyl 12-oxo-(*Z*)-8-dodecenoate (10) in 71 % yield. The sodium periodate oxidation of the  $\alpha$ -hydroxyketones in aqueous methanol solution was slow and gave a more complex mixture of products because the aldehyde function was partly converted to the dimethylacetal. Moreover, oxidation with sodium hydroperoxide proceeded with ring opening to the corresponding diacids 11 and 12 in 65 % yield. These acids were also produced in an approximately 3:1 ratio by sodium hydroperoxide oxidation of the crude mixture of diketones 8 and 9, obtained from the corresponding diols as described above; the overall yield was 70 %.

A Huang-Minlon modified Wolff-Kishner reduction of 10 took place with concomitant hydrolysis to the acid 13 in 86 % yield, and further reduction of the acid with lithium aluminium hydride afforded (*Z*)-8-dodecen-1-ol (1b) in 94 % yield. This was converted almost quantitatively to the acetate 1a. The spectral properties of both 1a and 1b were in agreement with those of the literature.<sup>5b,16</sup> All analytical data show that the products are free of any contamination by the corresponding *E* isomers.

Starting from the diol 2 the five steps synthesis depicted in scheme 1 provided stereochemically pure 1a and 1b in about 25 % overall yield, which compares well with those of the previously published routes to these compounds.

## EXPERIMENTAL

<sup>1</sup>H NMR spectra were recorded on a Varian EM 360 A spectrometer (60 MHz) and the <sup>13</sup>C NMR spectra were recorded on a Jeol JNM-FX 60 Fourier-transform spectrometer (15 MHz). The mass spectra were obtained on a Micromass 7070 F GLC/MS instrument. GLC analyses were carried out using 25 m capillary columns coated with either SP 1000 or SP 2100.

*trans*-(*Z*)-5-Cyclododecene-1,2-diol (3). A mixture of 20.0 g (0.1 mol), *trans*-(*Z*)-5,(*E*)-9-cyclododecadien-1,2-diol (2),<sup>17</sup> 17.5 g (0.35 mol) hydrazine hydrate and 1.0 g cupric sulfate in 500 ml methanol was heated at 60 °C with stirring, while 35.0 g (0.35 mol) of 35 % hydrogen peroxide was added during 90 min. After 3 h the mixture was filtered and the solvent evaporated under reduced pressure, leaving a crystalline residue. This was washed with water and dried to give 19.1 g (95 %) of a 3:1 mixture of the diol 3 and *trans*-cyclododecane-1,2-diol (4), respectively, m.p. 163–166 °C. The mixture could not be separated and spectral data refer to the mixture. GC-MS: *m/z* 198 (*M*<sup>+</sup> for 3). IR (KBr): 3303, 712 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  0.8–2.4 (compl.abs.) 3.60 (br.t.) 4.0 (br.s) 5.30 (m); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub> for 3:  $\delta$  21.8, 22.3, 23.3, 23.6, 25.6, 27.0, 34.3 (CH<sub>2</sub>), 68.2, 73.2 (CH-OH) 128.1, 130.9 (=CH-).

*Oxidation of the diols 3 and with N-chlorosuccinimide-dimethylsulfide (NCS-DMS). A solution of 15.0 ml (200 mmol) DMS and 25.0 g (187 mmol) NCS in 800 ml of dry toluene*

was stirred for 30 min. at 0 °C. A solution of the above diols 3 and 4 (28.5 g, 144 mmol) in 100 ml dry toluene was added rapidly and the mixture was stirred at 0 °C for 3 h. A solution of 20 g (198 mmol) triethylamine in 50 ml dry toluene was added dropwise and the mixture was allowed to attain room temperature. 400 ml of ether was added, the mixture filtered and the filtrate washed with 1 % aq. HCl and dried (MgSO<sub>4</sub>). Evaporation gave a residue which precipitated 4.3 g of diols by trituration with light petroleum. Distillation gave 21.5 g (90 % based on consumed diols) of a mixture of the  $\alpha$ -hydroxy ketones 5 and 6, 2-hydroxycyclododecan-1-one (7), and <5 % of the diketones 8 and 9.

(*Z*)-5-Cyclododecene-1,2-dione (8). To a stirred solution of 17.3 g (87 mmol) of the 3:1 mixture of 3 and 4, 150 ml DMSO, 150 ml benzene, 10 ml pyridine and 5 ml trichloroacetic acid, kept at 50 °C, 54 g (0.26 mmol) dicyclohexylcarbodiimide (DCC) was added. After 3 h the mixture was cooled and 70 ml of pet. ether and 15 g of oxalic acid were added in order to convert unreacted DCC to dicyclohexyl urea (DCU). When gas evolution had ceased, ice-water was added and DCU removed by filtration. The product was extracted with light petroleum and the extract washed with aq. NaHCO<sub>3</sub>, water and dried (MgSO<sub>4</sub>). Evaporation of the solvents gave 15.6 g of a 3:1 mixture of the dione 8 and cyclododecane-1,2-dione (9)<sup>18</sup> as a yellow oil which was used for the reduction step. The spectral data were obtained on a distilled sample, B.p. 56–58 °C (0.001 mmHg). IR (film): 1705, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (CCl<sub>4</sub>):  $\delta$  1.0–2.2 (m) 2.3–3.0 (m) 5.2 (m). <sup>13</sup>C NMR (CDCl<sub>3</sub>) for 8:  $\delta$  23.0, 24.1, 24.4, 26.7, 32.6, 37.3 (CH<sub>2</sub>), 128.1, 131.5 (=CH), 201.0, 201.5 (C=O).

2-Hydroxy-(*Z*)-5-cyclododecen-1-one (5). The above mixture of the diones 8 and 9 (15.6 g) was dissolved in 160 ml of DMF and 40 ml of water. After addition of 24 g (0.37 mol) of activated zinc dust,<sup>14</sup> the mixture was stirred at 80 °C for 15 h under N<sub>2</sub> and then cooled to room temperature. Powdered KOH (10 g) was added and stirring continued 90 min. The reaction mixture was filtered and the solid washed with 300 ml ether. The filtrate was diluted with 300 ml water and the product extracted with ether. The organic layer was washed with water, dried (MgSO<sub>4</sub>) and concentrated to give 13.9 g of product consisting of the  $\alpha$ -hydroxyketones 5 and 6 in a ratio of 93:7 (74 %) and 7 (24 %) and 8, 9 (2 %). A sample consisting essentially of 5 and 7 was obtained by recrystallization from ether/acetone, m.p. 64–66 °C. The spectral properties of 5 were obtained from the mixture by subtracting the data from an authentic sample of 7 (see below). 5: GLC-MS: *m/z* 196 (M<sup>+</sup>). IR (KBr): 3380, 1720, 710 cm<sup>-1</sup>. <sup>1</sup>H NMR (CCl<sub>4</sub>):  $\delta$  1.30 (br.s) 0.9–2.6 (compl. abs.) 3.43 (br. s), 4.22 (br. s), 5.24 (m). <sup>13</sup>C NMR (CCl<sub>4</sub>):  $\delta$  20.9, 22.0, 22.7, 23.5, 25.1, 27.5, 33.0, 33.2 (CH<sub>2</sub>), 75.8 (CH-OH), 128.1, 130.5 (=CH), 211.2 (C=O).

2-Hydroxycyclododecan-1-one (7) was prepared by oxidation of the diol 4 with the NCS/DMS complex, as described for 3, in 85 % yield, m.p. 73–74 °C. (lit.<sup>19</sup> 75 °C). MS: *m/z* 198 (M<sup>+</sup>). IR (CCl<sub>4</sub>): 3500, 1715 cm<sup>-1</sup>. <sup>1</sup>H NMR (CCl<sub>4</sub>):  $\delta$  1.40 (br.s. 16H), 1.65–2.55 (compl. abs. 4H) 3.25 (br.s. 1H) 4.27 (br.s. 1H). <sup>13</sup>C NMR (CCl<sub>4</sub>):  $\delta$  18.5, 21.2, 22.1, 22.3, 22.6, 23.8, 26.0, 30.6, 33.7 (-CH<sub>2</sub>-) 75.9 (CH-OH) 210.8 (C=O).

Methyl 12-oxo-(*Z*)-8-dodecenoate (10). The above mixture of 5 and 7 (10.3 g, 52 mmol) was dissolved in benzene-methanol (7:3) and cooled (10 °C). To the stirred solution 29 g (55 mmol) of 85 % lead tetraacetate was added portionwise during 45 min. After 4 h at room temperature 200 ml of ether was added, the organic phase separated and washed successively with 5 % aq. NaHSO<sub>3</sub>, 2 M Na<sub>2</sub>CO<sub>3</sub> and sat. aq. NaCl solution. The dried (MgSO<sub>4</sub>) solution was evaporated to afford 10.5 g of crude product. A solution of urea in methanol (250 ml, 0.1 g per ml) was added and after standing at -20 °C overnight the precipitated material was filtered. The procedure was repeated and distillation at 100 °C (0.001 mmHg) gave 6.35 g of oxoester 10, which contained 1 % of methyl 12-oxododecanoate (capillary GLC, SP 2100). Based on the amount of 5 in the starting material the yield was 71 %. MS: *m/z* 226 (M<sup>+</sup>). IR (film): 2716 (m), 1732 (s), 1725 (s), 716 (m), cm<sup>-1</sup>. <sup>1</sup>H NMR (CCl<sub>4</sub>):  $\delta$  1.38 (m, 8H), 1.8–2.7 (m, 8H) 3.61 (s, 3H) 5.30 (m, 2H) 9.65 (s, 1H); <sup>13</sup>C NMR (CCl<sub>4</sub>):  $\delta$  19.9 (-CH<sub>2</sub>CO-) 24.6, 26.9, 28.8, 29.2, 33.5, 43.5 (-CH<sub>2</sub>-) 50.7 (CH<sub>3</sub>-O) 127.5, 131.0 (=CH-) 172.2 (-O-CO-) 198.4 (-CH=O).

(*Z*)-8-Dodecenoic acid (13): To a solution of 2.2 g (10 mmol) of 10 and 1 g (20 mmol) of hydrazine hydrate in 10 ml diethylene glycol was added 1.5 g (27 mmol) of KOH and the mixture was heated under reflux for 1 h. Water and excess hydrazine hydrate were evaporated and the mixture heated at 200 °C for 3 h. When cold the mixture was acidified with HCl and extracted with benzene. The extract was washed with 1 N HCl and dried

(MgSO<sub>4</sub>). Evaporation of benzene gave 1.7 g (86 %) of the acid *13* as a liquid. IR (film): 3400, 1705 cm<sup>-1</sup>. <sup>1</sup>H NMR (CCl<sub>4</sub>): δ 0.85 (t, 3H) 1.30 (m, 10H) 1.8–2.4 (compl.abs., 6H) 5.21 (t, 2H) 10.40 (s, 1H).

(*Z*)-8-dodecen-1-ol (*1b*). To a solution of 1.7 g (8.6 mmol) of *13* in 100 ml of dry ether 0.7 g (18 mmol) of lithium aluminium hydride was added portionwise. After 1 h heating under reflux, the mixture was worked up in the usual way to give 1.5 g (94 %) of the alcohol *1b*. IR (film): 3325 cm<sup>-1</sup>. <sup>1</sup>H NMR (CCl<sub>4</sub>): δ 0.88 (t, 3H) 1.28 (m, 12H) 1.96 (m, 4H) 3.50 (t, 2H) 3.73 (s, 1H) 5.25 (t, 2H).

(*Z*)-8-dodecenyl acetate (*1a*) was prepared from 1.5 g (8.1 mmol) of *1b*, 0.75 g (9.4 mmol) of acetyl chloride and 10 ml of pyridine in the usual way. The crude product (1.8 g) was purified by chromatography (SiO<sub>2</sub>-CH<sub>2</sub>Cl<sub>2</sub>) to give 1.7 g (95 %) of the acetate *1a*. MS: *m/z* 226 (M<sup>+</sup>). IR (film): 1740, 1460, 1365, 1235, 1040 cm<sup>-1</sup>. <sup>1</sup>H NMR (CCl<sub>4</sub>): δ 0.90 (t, 3H) 1.35 (m, 12H) 2.00 (s, 3H) 2.00 (m, 4H) 4.06 (t, 2H) 5.33 (t, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 13.8 (CH<sub>3</sub>) 21.0 (methyl CH<sub>3</sub>) 22.9, 26.0, 27.2, 28.7, 29.2, 29.7 (CH<sub>2</sub>), 64.6 (CH<sub>2</sub>-O-), 129.7, 129.9 (=CH), 171.1 (C=O).

(*Z*)-4-Dodecen-1,12-diacid (*11*) and dodecane-1,12-diacid (*12*). a) From the hydroxyketones *5* and *7*. To a stirred solution of 2.0 g (10 mmol) of the above mixture of hydroxyketones *5* and *7* in 100 ml of methanol was added 2.0 g (50 mmol) of NaOH in 3 ml of water. 5.0 g (50 mmol) of 35 % H<sub>2</sub>O<sub>2</sub> was then added dropwise during 15 min. After 4 h at room temperature GLC analysis (SP 2100) showed that the starting material had been consumed. 100 ml of 5 % NaOH solution was added and most of the methanol evaporated under reduced pressure. Non-acidic products were extracted with ether and the aqueous phase acidified with 2 N HCl. Evaporation of the ether furnished 1.5 g (65 %) of the acids *11* and *12* as a 3:1 mixture, m.p. 92–95 °C. MS (CI): *m/z* 231, 229 (M<sup>+</sup>+1). IR (KBr) 3500–2400, 1705, 722 cm<sup>-1</sup>. <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>): δ 1.3 (m), 2.3 (m), 5.38 (m), 9.06 (m).

b) From the diketones *8* and *9*. To a stirred solution of the crude mixture of diketones *8* and *9*, obtained from 5.0 g (25 mmol) of the diols *3* and *4* as described above, in 220 ml of methanol 4.5 g (113 mmol) of NaOH in 7.5 mol of water was added. 11.2 g (115 mmol) of 35 % H<sub>2</sub>O<sub>2</sub> was added dropwise during 15 min, and after 3 h at room temperature the reaction was completed and it was worked up as described under a). 4.0 g (70 % based on the diols) of *11* and *12* was obtained as a 3:1 mixture, in all respect identical with that obtained from (a).

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